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UNIVERSITY OF ALBERTA

PYRIDINE AND REDUCED PYRIDINE ANALOGS OF OPIATE-LIKE ANALGESICS

BY

JOHN KWESI BUOLAMWINI

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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(MEDICINAL CHEMISTRY)

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"The conquest of pain remains, after all, the most important task, the main aim, and crowning - though yet distant - achievement of every medical man, at the bedside, in the operating theater, in the laboratory, on the battlefield, and wherever else mankind may suffer."

Cornelius Medvei.

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned hereby certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled PYRIDINE AND REDUCED PYRIDINE ANALOGS OF OPIATE-LIKE ANALGESICS, submitted by JOHN K. BUOLAMWINI in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY in Pharmaceutical Sciences (Medicinal Chemistry).

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ABSTRACT

The syntheses and pharmacological evaluation of novel pyridine and reduced pyridine heterocycles as analgesic agents have been investigated.

The regiospecific 1,3-dipolar cycloaddition reaction of 2-methyl-, 2-*n*-butyl- or 2-phenyl-1,2-dihydropyridines (**131a-c**), *N*-methyl-1,2-dihydropyridine (**131d**) or 1,2-dimethyl-, *N*-methyl-2-*n*-butyl- or *N*-methyl-2-phenyl-1,2-dihydropyridines (**131e-g**) with phenyl or *p*-chlorophenylsulfonyl azides (**132a, b**) was used to synthesize novel classes of 1,2,3,6-tetrahydropyridylidene-2-sulfonamides **134a-h** which were elaborated to 1,2,5,6-tetrahydropyridylidene- (**143a-g**) and piperidylidene-2-sulfonamides (**144a-h**). Similar reactions of 1-methyl-1,2-dihydropyridine (**131d**) with 2-(3- or 4-) pyridylsulfonyl azides (**146a-c**) afforded 1,2,3,6-tetrahydropyridylidene-2-(pyridyl)sulfonamides (**148a-c**) which were elaborated to piperidylidene-2-(pyridyl)sulfonamides (**150a-c**). Compounds **150b, c** were elaborated to *N*-acyl-1,6- and 1,2-dihydropyridyl analogs **152a-d** and **154a-e**, respectively.

New 1-methyl-4-propionyl-4-(pyridyl)piperidine analogs (**160a-c**) of ketobemidone and 1-methyl-4-ethoxycarbonyl-4-(pyridyl)piperidine analogs (**164a-c**) of meperidine and their 3-methyl derivatives **160d-h** and **164d, e, g, h, k , l** were also synthesized. 1,2-Dimethyl-4-ethoxycarbonyl-4-(pyridyl)piperidines **164f, i, j, m, l** were obtained from the reaction of *N*-2(-chloroethyl)-*N*-(2-chloropropyl)methylamine.(**162b**) with ethyl 2-, 3- or 4-pyridyl acetates (**163a-c**). The structures and stereochemistry of the 1,2- and 1,3-dimethylpiperidine esters **164d-n** were established by ^{1}H, ^{13}C and two dimensional heteronuclear shift correlated (^{1}H, ^{13}C) NMR spectrometry. Compounds **164b, c** were elaborated to the dihydropyridine analogs **169a-f** and **171a-m**, respectively.

1-[2-(Pyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidines (**179a-c**) were synthesized by the nucleophilic addition of 2- or 4-vinylpyridines (**173a, b**) to 1,4-dioxa-8-azaspiro[4.5]decane (**172**), and by the reaction of **172** with 3-pyridylethyl mesylate

(**174**), deketalization, Schiff base formation, sodium borohydride reduction and then acylation with propionic anhydride. Compounds **179b, c** were elaborated to the 1,6- and 1,2-dihydropyridyl analogs **180** and **181a-d**, respectively.

Analgesic activities for compounds **134a-g, 143a-g, 144a-h, 150a-c, 152a-d, 154a-e, 160a-h, 164a-d, g, h, j, k, l, n, 169c-f, 171a-m, 179a-c ,180** and **181a-d** were determined using the 4 % sodium chloride writhing assay in rats.

The analgesic test results for the tetrahydropyridylidene- and piperidylidene-2-aryloxysulfonamides **134a-g, 143a-g,** and **144a-h** which were designed as analogs of piperidylidene-2-arylsulfonamides (**124**), indicated that placing an oxygen atom spacer between the aromatic ring and the sulfur atom reduces analgesic activity. The analgesic activity profile for the aryloxysulfonamides was **144 > 143 > 134**.

The position of the pyridine ring attachment was an important determinant of analgesic activity for compounds **150, 160, 164** and **179** , which were more active than the dihydropyridine analogs.

The new 1-[2-(3-pyridyl)ethyl]norfentanyl, **179b**, was equipotent with fentanyl which is a potent clinical opioid analgesic. The dihydropyridinyl analogs **180** and **181a-d** showed a significantly lower toxicity relative to the corresponding pyridine analogs with respect to muscle rigidity. This new discovery offers a potential method for reducing toxicity of therapeutic agents possessing a pyridine ring.

Dedicated

to Patricia my wife

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1.0.0.0.0.0. INTRODUCTION

1.1.0.0.0.0. ANALGESICS

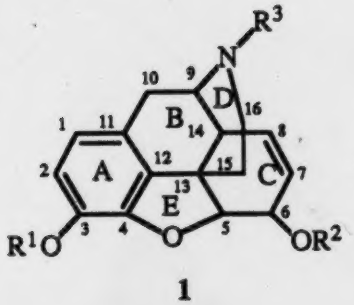
Pain, a physiological reaction to noxious stimuli, is a common unpleasant experience of all mankind, and efforts to control it date back to antiquity. Analgesics, more correctly referred to as analgetics, are drugs that reduce pain without affecting the consciousness of the individual.The analgesics in clinical use are divided into two categories, namely, analgesic-antipyretics[1], used to control mild pain, such as aspirin, and opioid analgesics[2], used to control moderate to severe pain, such as morphine. The latter category is the subject of this thesis.

1.1.1.0.0.0. Opioid Analgesics

Opium, the partially dried latex from the unripe seed capsules of *Papaver somniferum* L., was the first established analgesic drug.[3] In 1806 Serturner, a German pharmacist, isolated the principal active component of opium in crystalline form, which he named morphine, after the Greek goddess of dreams.[4] Morphine (**1a**) was the first alkaloid to be isolated, and is the prototype of the opioid (narcotic) analgesics. The natural alkaloids extracted from opium and semisynthetic congeners are termed opiates. The word opioid is the general term used to refer to all agents with morphine-like properties. The literature on opioid analgesics is vast! Recent reviews covering the structure-activity relationships of the diverse chemical entities that exhibit opioid analgesic activity are available.[3,5,6]

1.1.1.1.0.0. Morphine and other 4,5-epoxymorphinans

Morphine is the most prominent alkaloid, of the approximately fifty alkaloids, isolated from opium.[6] It has the structure **1a**,[7] with the systematic name (-)-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3, 6-diol. Its total synthesis was first accomplished by Gates and Tschudi.[8,9]



1

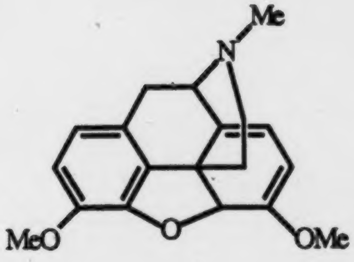
a, $R^1 = R^2 = H, R^3 = CH_3$

b, $R^1 = CH_3, R^2 = H, R^3 = CH_3$

c, $R^1 = R^2 = H, R^3 = CH_2CH{=}CH$

d, $R^1 = R^2 = COCH_3, R^3 = CH_3$

e, $R^1 = R^2 = H, R^3 = CH_2CH_2Ph$



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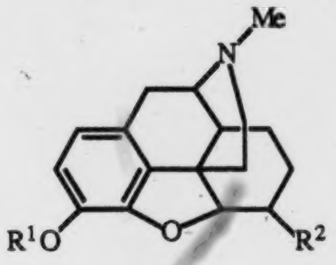


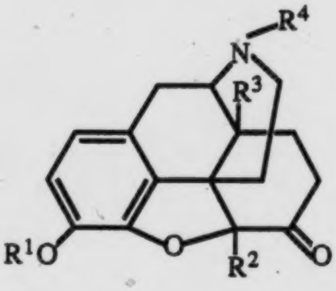
3

a, $R^1 = CH_3, R^2 = OH$

b, $R^1 = H, R^2 = N_3$

The high dependence liability and abuse rate of morphine, in addition to its deleterious side effects of respiratory depression, constipation, nausea and vomiting,[10] prompted an intensive search for a better analgesic.[11,12] Codeine (**1b**) is the second most important analgesic constituent of opium. It has about one tenth the activity of morphine in man, with a lower dependence liability. Acetylation of morphine affords the diacetyl derivative, (**1d**), known as heroin, which has twice the analgesic potency of morphine. Heroin is more addictive than morphine, and has a higher incidence of abuse.[13-15] Hydrocodeine (**3a**), hydrocodone (**4a**) and hydromorphone (**4b**) are also useful clinical analgesics.[16] Azidomorphine (**3b**) has been prepared by displacement of the C-6 tosylate or mesylate of morphine, with azide anion. It is forty to fifty times more potent than morphine, in man, with a lower addiction liability.[17,18] This is in contrast to morphine, in man, with a lower addiction liability.[17,18] This is in contrast to the general observation that an increase in analgesic activity is accompanied by an increase in addiction liability.

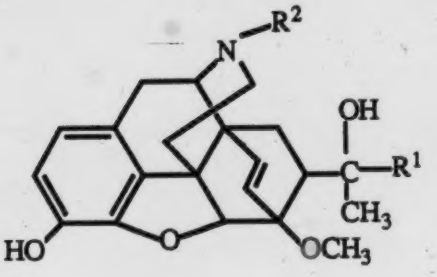
Metopon (**4c**),[18,19] with about three times the analgesic potency of morphine, is noted for lower respiratory depressant and emetic side effects. N-Substituent changes resulted in compounds with mixed agonist and antagonist activity. Nalorphine (**1c**),[20] with an allyl group replacing the N-methyl group of morphine, is a morphine antagonist which also has analgesic activity in man. Its use as an analgesic is however discouraged by psychotomimetic side effects. A phenethyl group in place of the N-methyl group (**1e**) increases analgesic agonist activity considerably without any antagonist effect.[21]



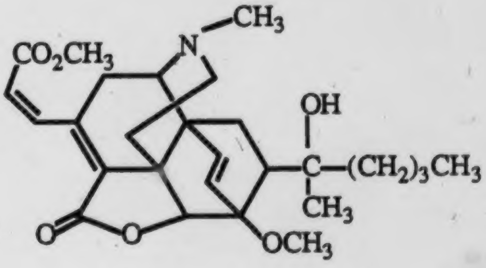
4

a, $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$
b, $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
c, $R^1 = H$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$
d, $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = CH_3$
e, $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = CH_2CH{=}CH_2$

Oxymorphone (**4d**), with a hydroxyl group at C-14, is the most potent clinically used morphine surrogate, but its dependence liability parallels analgesic activity.[16] The N-allyl analog of oxymorphone, known as naloxone (**4e**), was the first pure opioid antagonist (that is an antagonist without any analgesic agonist activity in both animals and man). It is about fifteen to thirty times more potent than nalorphine as an antagonist[22], and is used clinically and as an opioid research tool. Ethorphine (**5a**) is about one thousand times more potent than morphine. It is representative of a group of potent Diels-Alder adducts of thebaine (**2**), referred to as oripavines.[23-26] An interesting observation, in light of the structure-activity relationships of opioid analgesics, is that compound **6**, an analog of ethorphine lacking an aromatic ring, exhibits analgesic activity comparable to morphine.[27] N-Substituent modifications in the oripavines show a similar pattern to corresponding modifications in the morphine derivatives. Thus buprenorphine (**5b**) is a clinically useful narcotic agonist-antagonist analgesic (compare nalorphine).[28] Reviews on the SARs of this group of opioid analgesics have been published.[29-32]


R^2
N
OH
C
R^1
CH$_3$
HO
O
OCH$_3$

5


CH$_3$
CO$_2$CH$_3$
N
OH
C—(CH$_2$)$_3$CH$_3$
CH$_3$
O
O
OCH$_3$

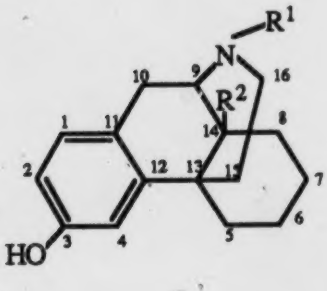
6

a, R^1 = (CH$_2$)$_3$CH$_3$, R^2 = CH$_3$

b, R^1 = C(CH$_3$)$_3$, R^2 = CH$_2$—◁

1.1.1.2.0.0. Morphinans

The morphinans are synthetic tetracyclic hexahydrophenanthrene derivatives (7) lacking the 4,5-epoxy bridge of morphine and its derivatives.


R^1
N
16
10
9
R^2
1
11
14
8
2
12
13
15
7
6
5
HO
3
4

7

a, R^1 = CH$_3$, R^2 = H

b, R^1 = CH$_2$CH=CH$_2$, R^2 = H

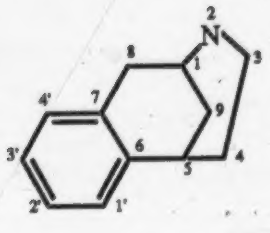
c, R^1 = CH$_2$—◁ , R^2 = OH

d, R^1 = CH$_2$—◇ , R^2 = OH

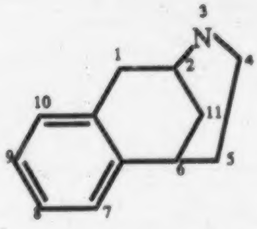
Levorphanol ((-)-**7a**) is eight times as potent as morphine as an analgesic, and is used clinically, even though it is no better than the latter in terms of dependence liability. Its (+)- antipode, dextrophan ((+)-**7a**) is devoid of analgesic activity.[33] The synthesis of morphinan analgesics has been reviewed.[5] Many synthetic routes employ the Grewe cyclization.[34] Morphinans that are directly related to morphine have a *cis* B/C ring fusion. Those that have a *trans* B/C ring junction are known as isomorphinans and are generally more active than the former compounds.[5,6] Again N-substituent modifications show a similar pattern to the morphine class with regard to agonist and antagonist activities. A change from opioid agonist to antagonist or mixed agonist-antagonist occurs[36] on replacement of the N-methyl substituent by an allyl, a cyclopropyl- or cyclobutylmethyl group. Levallorphan (**7b**) is a clinically useful morphine antagonist whereas oxylorphan (**7c**) and butorphanol (**7d**) are potent mixed agonist-antagonists.[37] The structure activity-relationships of morphinans have been reviewed.[5,6,38,39] The presence of a C-3-OH group confers higher levels of analgesic potency similar to that in the morphine series. Methylation of the C-3 OH decreases activity. N-Phenethyl,[40] and N-heteroarylethyl groups [41] increase analgesic potency. N-β -Cyanoethyl derivatives were also found to have good analgesic activity.[42]

1.1.1.3.0.0. Benzomorphans

Two nomenclature systems have been used in benzomorphan chemistry. The more common trivial nomenclature refers to them as 6,7-benzomorphans (**8**), but they are systematically named as 1,2,3,4,5,6-hexahydro-2, 6-methano-3-benzazocines (**9**).

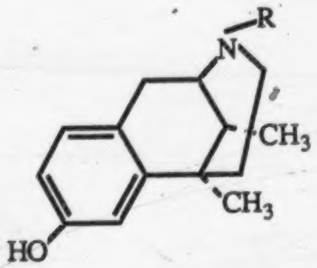


8



9

The archetype of this group is pentazocine (**10a,** Talwin, Sosegon, Fortral). It is an agonist-antagonist analgesic in clinical use with a low dependence liability, but associated with undesirable psychotomimetic side effects.[43,44] The synthesis of benzomorphans has also been reviewed.[5,34,45] Tetralone [46] or an appropriately substituted pyridine [47] precursor are the respective starting materials for the two principal routes to benzomorphans.



a, R = $CH_2CH{=}C(CH_3)_2$

b, R = CH_2CH_2Ph

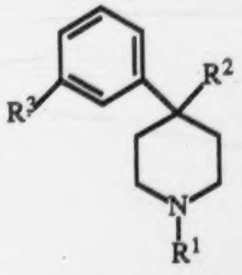
10

The configuration at the C-11 (**9**) is important. A β-oriented Me, Et or *n*-Pr group exhibits about five times the analgesic activity of the α-epimer. N-Substituents such as cyclopropylmethyl, allyl and cyclobutylmethyl, exhibit agonist-antagonist activity, whereas N-phenethyl compounds display enhanced agonist activity. For example phenazocine (**10b,** Narphen) is six times more potent than its N-methyl analog.[48] Other general correlations in the SARs of benzomorphans are: 1) an 8-OH (structure **9**) enhances activity even though it is not necessary for analgesic activity, in contrast to the morphine series, it can be replaced by an amino group without loss of activity,[49] 2) analgesic activity is increased by substituting a lower alkyl group such as ethyl or propyl at C-6 (**9**), 3) introduction of a keto group at C-1 provides mixed agonist-antagonists, 4) unlike the morphine and morphinan series, introduction of a C-11-OH , analogous to the potency enhancing C-14 OH group in morphine, is not associated with strong analgesia,[50] however, β-orientated OH groups enhance antagonist activity, and 5) heteroarylethyl N-substituents increase analgesic activity.[51]

A major disadvantage to the clinical use of benzomorphan agonist-antagonist analgesics is the occurrence of psychotomimetic side effects, believed to be the result of their interaction with the opioid σ-receptor.[52]

1.1.1.4.0.0 4-Phenylpiperidines

The accidental discovery of the opioid analgesic meperidine (**11a**, pethidine, Demerol) by Eisleb and Schaumann fifty years ago, began the era of this class. Meperidine is the most widely used synthetic opioid analgesic. It ranks between codeine and morphine in potency,[54] and is particularly useful in situations involving smooth muscle spasm. Its toxicity is low and tolerance develops slowly. The dependence liability of meperidine is lower than that of morphine.[55] The usual side effects of morphine are observed with meperidine in addition to the induction of seizures[56] in some patients. Full clinical and pharmacokinetic profiles of meperidine have been published.[57-60] Meperidine is more lipophilic than morphine.[61] Its receptor affinity is lower than expected from its activity.[62,63]



11

a, $R^1 = Me$, $R^2 = CO_2Et$, $R^3 = H$

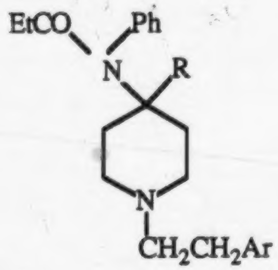
b, $R^1 = Me$, $R^2 = COEt$, $R^3 = OH$

c, $R^1 = Me$, $R^2 = OCOEt$, $R^3 = H$

Eisleb's[64] original synthesis of meperidine is still in use in addition to subsequent modifications described by other workers.[65,66] The ketone analog of meperidine known as ketobemidone (**11b**),[67] is ten to twelve times more active[60] and possesses a high dependence liability. Analogs of meperidine in which the ester function is reversed (**11c**, reversed ester series)[71,72] exhibit higher analgesic activity than their ester isomers.

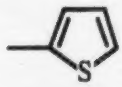
1.1.1.5.0.0. 4-Anilidopiperidines

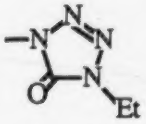
Fentanyl (**12a**, Sublimaze, Leptanol) is the prototype of this class of potent analgesics. It is characterized by a potency 500 times that of meperidine in mice, a rapid onset and a short duration of action.[70-72] It is used primarily in neuroleptanalgesia.[73,74] Tollenaere *et al* [75] have summarized the important SARs for fentanyl. Analogs of fentanyl in clinical use include surfentanyl (**12b**)[76], alfentanyl (**12c**)[77] and carfentanyl (**12d**).[78,79] The first series of fentanyl analogs exhibiting opioid antagonist activity were only recently reported.[80]



12

a, R = H, Ar = Ph

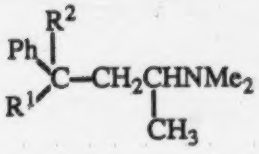
b, R = CH_2OMe, Ar = 

c, R = CH_2OMe, Ar = 

d, R = CO_2Me, Ar = Ph

1.1.1.6.0.0. Methadone and related compounds

Methadone (**13a**, amidone, Physeptone) is representative of the 3,3-diphenylpropylamine analgesics. It is used clinically as the racemate, which is equipotent with morphine. However, unlike the latter, it is orally active and causes less severe withdrawal symptoms. It is the drug of choice for treating opioid addicts.[57,81]



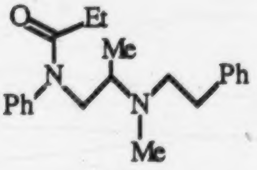
a, R^1 = Ph, R^2 = COEt

b, R^1 = CH_2Ph, R^2 = OCOEt

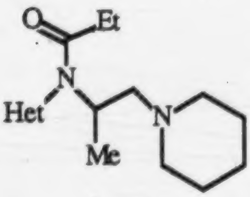
13

A monograph covering the early chemistry and pharmacology of diphenylpropylamine analgesics has been published.[82] Their SARs are also included in recent reviews on opioid analgesics.[3,5,6] Racemic propoxyphene (**13b**) is an orally active methadone analog with half the analgesic activity of meperidine, that is used to relieve mild pain.[83]

N-Phenylpropionamide derivatives have also been found to exhibit opioid analgesic activity. Diampromide (**14**) is the most notable. It has an analgesic potency between that of morphine and meperidine. The (+) - antipode is more active.[84] Propiram (**15a**) and its analogs show mixed agonist and antagonist activities.[85] The 2-pyridyl compound (**15a**) is the most potent agonist followed by the 3-pyridyl analog(**15b**), whereas the 4-pyridyl compound (**15c**) is inactive.[86]



14



15

a, Het = 2-pyridyl

b, Het = 3-pyridyl

c, Het = 4-pyridyl

1.1.1.7.0.0. Enkephalins and other endogenous opioid peptides

Met-enkephalin (**16**) and leu-enkephalin (**17**) are pentapeptide opioids that were first isolated from pig brain.[87,88]

Tyr-Gly-Gly-Phe-Met (OH) Tyr-Gly-Gly-Phe-Leu(OH)

16 **17**

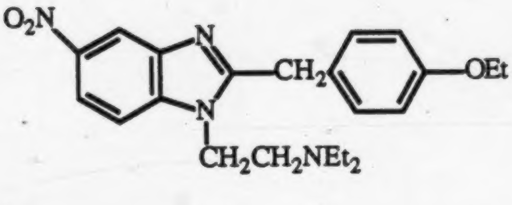
Enkephalins are less potent and have a shorter duration of action than morphine.[89] Met-enkephalin is slightly more active than leu-enkephalin. The short duration of action is attributed to their rapid degradation by enkephalinase, which cleaves the Gly^3-Phe^4 bond of enkephalins.[90] Thiorphan (DL-3-mercapto-2-benzylpropanoylglycine) inhibits enkephalinase.[91] The resistance of enkephalins to enzyme attack can be increased by substituting D-amino acids for Gly^2 or by converting the terminal carboxyl group to an amide.

Other endogenous opioid peptides isolated from the pituitary gland include β-endorphin [92] (20 times the potency of morphine) and dynorphine.[93] Numerous opioid peptides have been isolated since the discovery of the enkephalins.[109] Their receptor selectivity and SARs have been summarized.[5,6] The molecular conformations of these highly flexible compounds have been investigated extensively.[5,95] Opioid peptides have not been used clinically due to their undesirable side effects such as feelings of warmth, heaviness in the legs and increased bowel movements.[96]

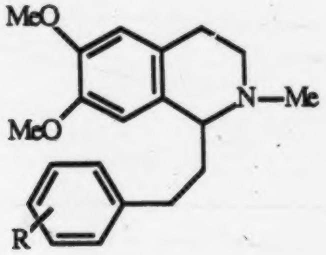
1.1.1.8.0.0. Miscellaneous groups of opioid analgesics

1.1.1.8.1.0. Benzimidazoles

The benzimidazoles have the historic significance of being the first group of narcotic analgesics to exhibit activity many orders of magnitude higher than that of morphine. Etonitazene (**18**) , which is the most important member of this group, was found to be 1,500 times as active as morphine in mice.[97] They are not in clinical use because of high dependence liability.



18



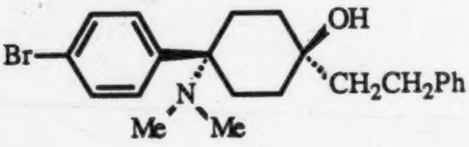
19

1.1.1.8.2.0. Tetrahydroisoquinoline derivatives

1-Phenethyltetrahydroisoquinolines (**19**) possess analgesic properties similar to codeine. Methopholine (**19,** R= 4-Cl) was investigated in clinical trials. A report on this group is available.[98]

1.1.1.8.3.0. Cyclohexane derivatives

The first report on cyclohexane opioid analgesics came from the Upjohn Co. in 1979.[99] The only compound in that report (**20**), displayed analgesic activity 10,000 times that of morphine.



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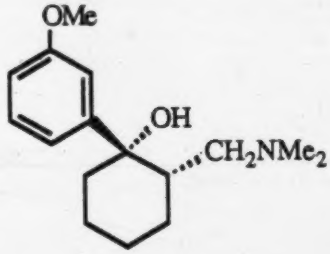

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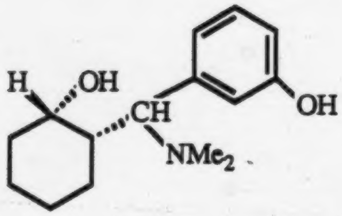

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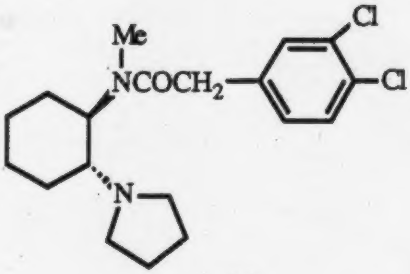

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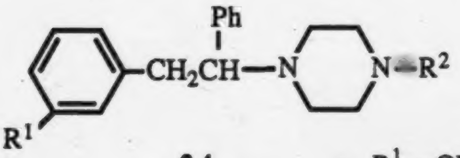
Other important cyclohexane analgesic agents are tramadol (**21**),[100] and ciramadol ((-)-**22**).[101] More recently cyclohexylbenzeneacetamides such as U-50,488 (**23**)[102] have been developed as one of the most selective groups of κ-receptor agonists.

1.1.1.8.4.0. Piperazines

The piperazine ring system is a common structural feature of analgesics represented by structure **24**.[103] Some of these (**24a**) have recently been described as having mixed agonist-antagonist properties with low dependence liability.[104]

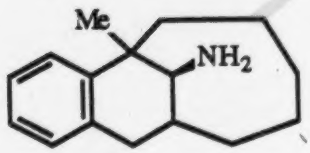


24

a, $R^1 = OH$, $R^2 = CH_2CH{=}C(CH_3)_2$

1.1.1.8.5.0. Aminotetralins

The most important member of this group is dezocine ((-) -**25**), which exhibits analgesic potency in the morphine range.[105] The unique feature of the group is that the amine function is primary.



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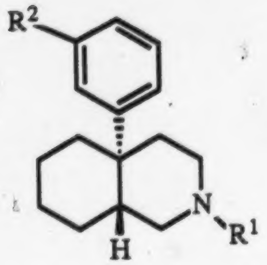


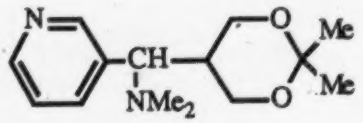
26 **a**, R^1 = Me, R^2 = OH

1.1.1.8.6.0. *trans*-Aryldecahydroisoquinolines

N-Substituted derivatives of *trans*-aryldecahydroisoquinolines (**26**) have recently been reported to be opioid analgesics with high affinities for μ- and κ-opioid receptors. Compound **26a** is three times as active as morphine.[106]

1.1.1.8.7.0. Doxpicomine series

A series of acetals represented by doxpicomine (**27**) have also shown potent morphine-like analgesic activity.[107]



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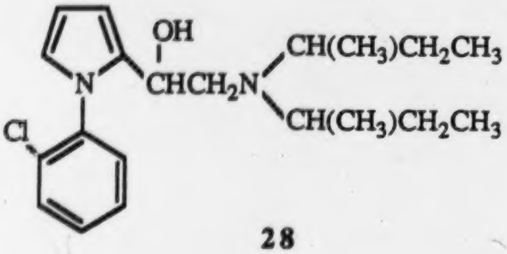
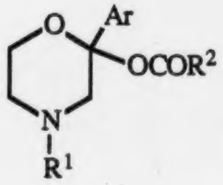
1.1.1.8.8.0. Pyrrole and morpholine derivatives.

Viminol (**28**) is a pyrrole derivative which is a mixture of three diastereoisomers. The most potent of these diastereoisomers is five times as active as morphine in rats.[108]

Morpholine analogs , (29) related to the phenylpiperidine analgesics, with potent analgesic activity have been reported.[109]


OH
CHCH₂N
CH(CH₃)CH₂CH₃
CH(CH₃)CH₂CH₃
N
Cl

28


O
Ar
OCOR²
N
R¹

29

1.1.1.9.0.0. The opioid analgesic pharmacophore

The initial proposals for the structural requirements of opioid analgesics[110] have not stood the test of time. The prerequisites for all authentic opioid analgesics, in spite of the wide variation in size, molecular skeleton and functionalities, are the presence of a basic center with a pKa that allows extensive protonation at physiological pH, and an aromatic feature.[5] The basis for a common pharmacophore stems from the observation that all the structures have the potential to allow simultaneous overlap of the amine nitrogen and an aromatic group.[111]

1.1.1.9.1.0. Molecular modelling and quantitative structure-activity relationships (QSARs)

The molecular modelling and QSARs of opioid analgesics have been reviewed.[6] Molecular mechanics programs such as Allinger's MM2 program[112] have been utilized in molecular modelling studies.[113] X-Ray crystallographic studies show that all morphine derivatives have a "T" shape in which rings A and B constitute the vertical part of the T and rings C and D the horizontal part. The piperidine ring is in a chair conformation with the N-substituent equatorial. The C-ring conformation depends on the presence or absence of the 7,8-double bond and C-6 substituents. Whereas the rigid analgesics such as morphine have the phenyl ring in an axial conformation, the flexible phenylpiperidines prefer an equatorial phenyl ring.[113] Conformational comparisons between the enkephalins and rigid opioids have also been made.[114,115] Quantum chemical[116,117] and classical linear free energy descriptors[118] have both been applied to the QSARs of opioid analgesics.

1.1.1.10.0. Opioid receptors

The existence of opioid receptors was confirmed in 1973 through stereospecific ligand binding experiments with rat brain homogenates using [^{3}H]ethorphine,[119] [^{3}H]naloxone[120] and [^{3}H]morphine.[121] A comprehensive monograph[122] on opioid receptors has recently been published. These receptors are protein in nature and cerebroside sulfate is said to be a necessary integral part of the μ-receptor.[123]

1.1.1.10.1.0. Multiple opioid receptors

Shortly after the discovery of opioid receptors, Martin *et al* [124] proposed the occurrence of multiple opioid receptors. Four of these, namely, mu (μ), kappa (κ), delta (δ) and sigma (σ) have been well demonstrated. There is evidence for other receptor types as well. These include epsilon (ε),[125] iota (ι)[126] and lambda (λ).[127] Subclasses among the major receptor types have also been characterized, for example μ_1 and μ_2,[128,129] and κ_1 and κ_2.[130] The characterization of multiple opioid receptors has been reviewed.[131] In addition to brain, several peripheral tissues contain opioid receptors which are used to study the receptor selectivity of opioid receptor ligands. μ-Receptors predominate in guinea pig ileum, δ-receptors in mouse vas deferens, κ-receptors in rabbit vas deferens and ε-receptors in rat vas deferens. Species differences in the proportions of μ-, δ-, and κ-receptors have also been observed.[132] The mediation of analgesia by multiple opioid receptors has been recently reviewed.[133]

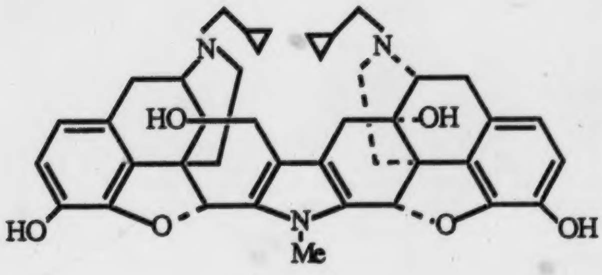
The ultimate proof of the existence of different opioid receptors will be the identification of different genes that encode different opioid receptor proteins.

1.1.1.10.2.0. Agonist and antagonist ligands

The interaction of opioid receptors with selective agonists elicit pharmacological responses typical of the receptors (Table 1). Selective antagonists are also available. Guanine nucleotides are known to decrease agonist binding.[134] Sodium ions also decrease agonist binding, and κ- sites are less sensitive to sodium than are μ- and δ-sites.[134]

No endogenous opioid antagonists have yet been reported, but evidence exists to show that the peptides MIF-1(Pro-Leu-Gly) and Tyr-MIF-1 (Tyr-Pro-Leu-Gly) are endogenous opioid antagonists.[142] The requirements for μ versus δ selectivity of enkephalins have been delineated.[143]

The bivalent ligand approach of Portoghese's group, [144] has led to the development of highly selective κ- antagonists like binaltorphimine (**30**). Interestingly, the benzodiazepine tifluandom (**31**) is also a selective κ- agonist.[145] The most potent derivatives of fentanyl exhibited negligible preference for μ- or δ-sites whereas the least potent analogs such as alfentanyl, showed an extremely high selectivity for μ-receptors.[146]



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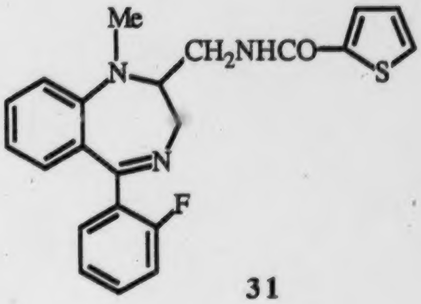

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Table 1: Selective Agonist and Antagonist Ligands and Phamacological Profiles of Major Opioid Receptors

Receptor	Agonists	Antagonists	Pharmacology	References
μ_1	morphine, DAGO.[a]	naloxazone	analgesia	128,135,136.
μ_2	morphine	naloxone	respiratory depression	128,135,137.
δ	enkephalins, DADLE.[b]	naltrindole	analgesia	137-139.
κ	dynorphine, U50,488	binaltorphimine	analgesia, diuresis	137,140,141.
σ	(-)-allylnormetazocine	naltrexone	psychotomimetic effects	137

[a] DAGO = Tyr-DAla-Gly-MePhe-Gly-ol.

[b] DADLE = DAla^2-DLeu^5-enkephalin.

1.1.1.10.3.0. Receptor models and factors influencing affinity and intrinsic activity.

The opiate receptor topology was first proposed by Beckett and Casy [110] based on the rigid (-)-morphine molecule. The three sites described were: 1) a flat region that permits binding with the aromatic ring, with a site close by to bind the phenolic OH, 2) an anionic site to associate with the protonated basic nitrogen and 3) a cavity to accommodate the $-CH_2-CH_2-$ chain linking the nitrogen and the quaternary carbon, C-13 (Fig. 1).

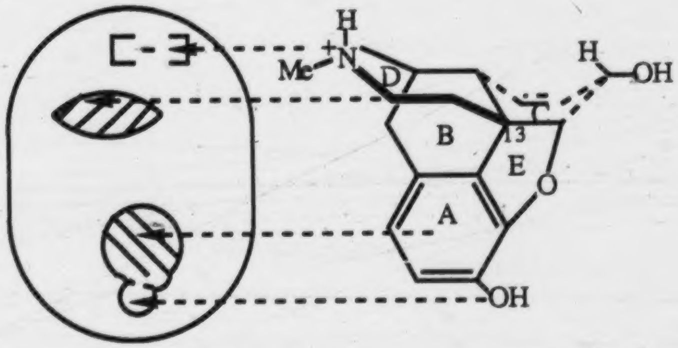


Fig. 1: Diagrammatic representation of the receptor topology corresponding to the binding features of protonated (-)-morphine.[5] The dashed arrows show complementary elements of the receptor and the ligand.

The failure of the above model to account for the activities of compounds discovered subsequently led to other proposals which have been reviewed.[5] A recent model by Kolb[147] suggests that agonist activity (intrinsic activity) results from a proton transfer operation from the protonated nitrogen of the bound ligand to the receptor. This proton transfer is dependent upon stereoelectronic factors resulting mainly from the N-substituents. In light of this model, the previously held view[148] that the direction of the nitrogen lone-electron pair was the critical determinant of agonist activity should be discarded. N-Substituents of agonists allow an easy proton transfer whereas those of antagonists block the process. The N-substituents of agonists-antagonists are imperfect blocking devices. Depending on the size and conformation of other groups on the molecule, blocking could occur in compounds with so called traditional agonist N-substituents such as methyl[149] or phenethyl. In another attempt to rationalize the agonist-antagonist behavior of certain opioids, Cheney[150] has reported that charge-transfer contributions involving an allyl-like substituent as an electron acceptor, were found to be far more important for binding in the antagonist than in the agonist state. The relationship between N-dealkylation of opioid agonists and the events leading to analgesic response is still unclear.[151, 152] The biochemical events leading to analgesia are still under investigation but the inhibition of adenylate cyclase has been implicated.[153]

1.1.1.11.0.0. Other pharmacological effects of opioids

The biological effects of opioids have been reviewed.[154] Martin[155] has also reviewed the pharmacology of opioid analgesics. The non-analgesic and behavioral studies of opioid peptides in 1986 and 1987 have been reviewed.[156, 157] The well documented pharmacological effects of opioids other than analgesia are: antitussive,[158] inhibition of gastrointestinal tract (GIT) motility,[159] respiratory depression, emesis, euphoria, miosis, dysphoria, sedation, mydriasis, tolerance, dependence and enhancement of appetite.

1.1.1.11.1.0. Opioid addiction

Tolerance and dependence (psychological and physical) have been the most important deterrents to the use of opioid analgesics. Withdrawal symptoms [2] have been found to differ with the type of opioid receptor involved.[157] The immune system is believed to be involved in opioid dependence.[160] It has therefore been suggested that modulation of the immune system could result in a better treatment for opioid addiction than methadone substitution.[161] A strategy to circumvent the problem of addiction may be to use enkephalinase inhibitors, such as thiorphan,[91] as analgesics.

1.1.2.0.0.0. Analgesic Testing

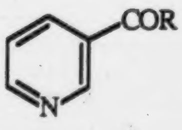
The many experimental protocols used for analgesic testing have been reviewed.[162, 163] They all involve the application of noxious stimuli to animals and determination of the ability of the test compound to protect the animal against these stimuli. The assays utilize chemical (writhing),[164] thermal (hot plate),[165,166] electrical (shock titration)[167] and pressure[168] stimuli. For an analgesic compound to be classified as a μ-opioid , its analgesia must be reversible by naloxone. The evaluation of analgesics in man has also been reviewed.[169]

1.2.0.0.0.0. PHARMACOLOGICAL APPLICATIONS OF PYRIDINES AND REDUCED PYRIDINES

The pharmacology of pyridines and reduced pyridines has been reviewed.[170] These heterocycles have great therapeutic value and potential.

1.2.1.0.0.0. Pyridines

Next to piperidine, the pyridine ring is the most frequently encountered heterocycle in pharmaceutical agents.[171] Pyridine compounds most frequently display eight types of pharmacological activity.[172] These include antitubercular, antihistaminic, (H_1-receptor antagonists), vasodilative, anticholinestererase, analgesic, antiinflammatory, hypotensive and antitumor activities.



32

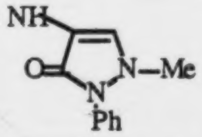
a, $R = OH$

b, $R = NH_2$

c, $R = OCH_2Ph$

d, $R = N(C_2H_5)_2$

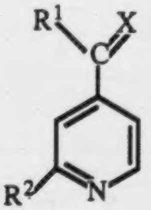
e, R =



f, $R = O(CH_2)_2N(C_2H_5)_2$

g, $R = O(CH_2)_2O_2CCH(CH_3$

Nicotinic acid (**32a**) and its derivatives are used clinically as vasodilators (**32a**, **32f**), antiarteriosclerotics (**32a**, **32g**), antilipidemics (**32a**, **32g**), vitamins (**32a**, **32b**), antirheumatics (**32e**), analeptics (**32d**) and hyperemics (**32c**).[171] Isonicotinic acid derivatives have been studied extensively as tuberculostatics (**33a**-**d**). The hydrazide iproniazid (**33b**) also has useful monoamine oxidase inhibitory activity. Numerous pyridine containing compounds are in clinical use as antihistamines. Notable among these are mepyramine (**34**, Anthisan[R]) and dexchloropheniramine ((+)-**35**, Piriton[R]).



33

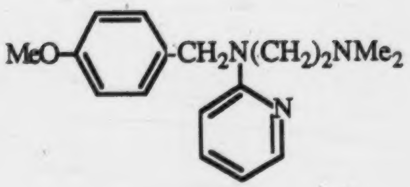
a, $X = O, R^1 = NHNH_2, R^2 = H$

b, $X = O, R^1 = NHNHCH(CH_3)_2, R^2 = H$

c, $X = S, R^1 = NH_2, R^2 = i\text{-}Pr$

d, $X = S, R^1 = NH_2, R^2 = H$

Recently developed nonglycoside and noncatecholamine inotropic agents such as amnirone (**36**) and milnirone (**37**) are used in congestive heart failure; they offer many advantages over glycosides and catecholamines.[173]



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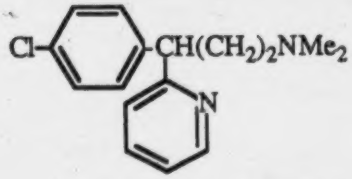

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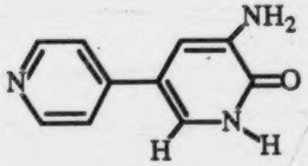

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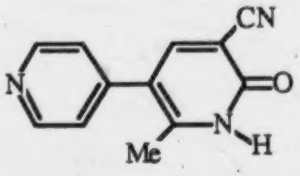
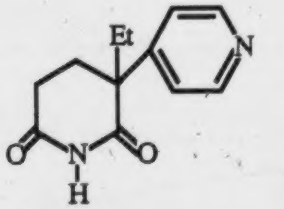


37

3-Phenoxypyridines are being investigated as anticonvulsant agents[174] and 2-piperazinylpyridines have been reported to be useful in the treatment of Parkinson's disease.[175] 3-Ethyl-3-(4-pyridyl)piperidine-2,6-dione (**38**), an analog of aminoglutethimide (**39**), is presently undergoing clinical trials for the treatment of hormone-dependent breast cancer .[176] Orally active antiallergic 3-pyridylacrylamides have also been reported.[177]



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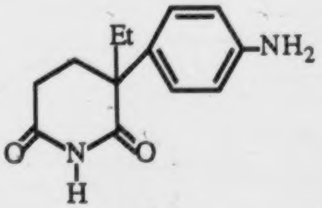

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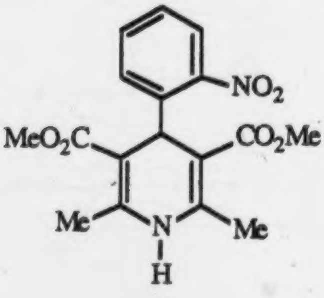
1.2.2.0.0.0. Dihydropyridines

Nifedipine (**40**, Adalat) is the prototype of the extensively investigated 4-aryl-1,4-dihydropyridine calcium channel blockers that are used as antianginal drugs.[178] An extensive bibliography on the biological properties of dihydropyridines has been included in the appendix to Kuthan and Kurfusth's review on the chemistry of dihydropyridines.[179]



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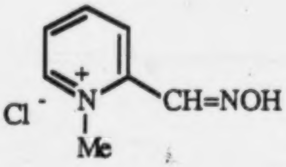

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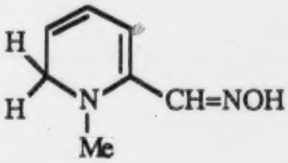

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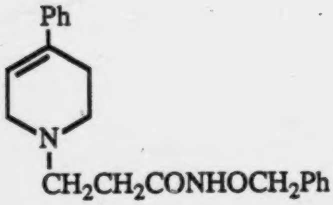
The enhanced lipophilicity and the ease of aromatization of dihydropyridines to pyridinium salts have been exploited in the prodrug concept to deliver drugs to the brain. Thus N-methylpyridinium-2-carbaldoxime (**41**,2-PAM), the drug of choice in organophosphate poisoning, is delivered to the brain by the dihydropyridine prodrug analog **42**. [180] This concept has been used to deliver amines, catecholamines and steroidal hormones to the brain.[181] Success is also being achieved in using this redox system to deliver anti-AIDS (acquired immunodeficiency syndrome) virus nucleosides to the brain of animals, with potential for the treatment of AIDS dementia complex.[182] Significant improvement in antipyretic activity, and distribution of naproxen and indomethacin, was achieved in rats using this dihydropyridine-pyridinium salt redox system.[183]

1.2.3.0.0.0. Tetrahydropyridines

1,2,3,6-Tetrahydropyridines are the most frequently encountered class of pharmacologically active partially-reduced pyridine compounds. The most prominent pharmacological effects of tetrahydropyridines are hypotensive and analgesic activities.[170,184] Compounds **43** and **44** exhibit hypotensive activity.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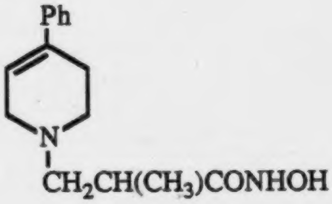
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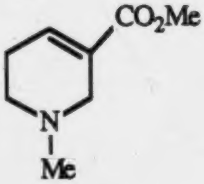
The areca alkaloid arecoline (**45**), obtained from *Areca catechu* , is a cholinergic agent also exhibiting mild hypotensive activity. It is used as a diaphoretic and an anthelmitic.[185] Isoarecoline methiodide (**46**) is reported to be one of the most potent nicotinic agonists known.[186]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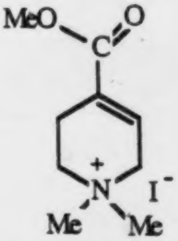
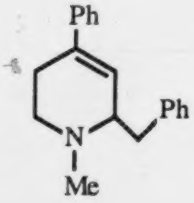

46

Compound **47** and its derivatives were synthesized as benzomorphan analogs, which exhibited significant analgesic activity and a low dependence liability.[187] *N*-Carbonylamino-1,2,3,6-tetrahydropyridines (**48**) also exhibited analgesic and antiinflammatory activities.[188] Similar compounds have been recently reported to possess analgesic and hypergylcemic activities.[189]



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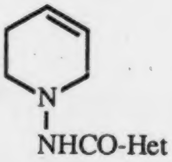
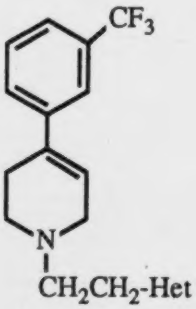


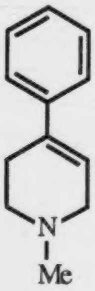
48

Het = 2-, 3-, 4-pyridyl

The anorexiant properties of compounds **49** have been reported.[190] 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, **50**, MPTP, a well documented neurotoxin,[191] is used in a mouse animal model for studying Parkinsonism.[192] Its pharmacology has been reviewed.[191]



49 Het = 2-, 3-, 4-pyridyl



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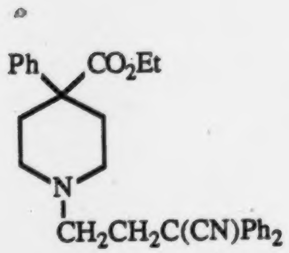
1.2.4.0.0.0. Piperidines

The piperidine ring is the most commonly occurring heterocycle present in pharmaceutical agents.[171] It is most characteristic in opioid analgesics such as meperidine, antidiarrheals such as diphenoxylate (**51**, Lomotil) and neuroleptics such as haloperidol (**52**, Haldol).



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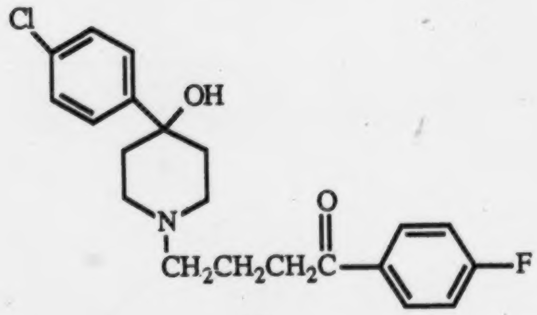
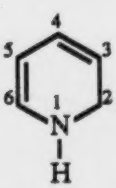


52

1.3.0.0.0.0. THE CHEMISTRY OF DIHYDROPYRIDINES

Three reviews[179, 193,194] have been published which review the synthesis, physical and chemical properties and reactions of dihydropyridines. Theoretically five isomeric dihydropyridines are possible; 1,2-(**53**), 1,4-(**54**), 2,3-(**55**), 2,5-(**56**) and 3,4-dihydropyridine (**57**). The parent dihydropyridines (**53** - **57**) are very unstable. To date only the 1,4-isomer (**54**) has been isolated, but it decomposes rapidly in air.[195]



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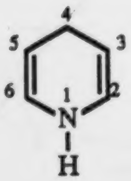

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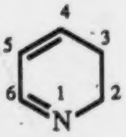

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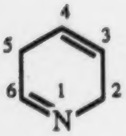

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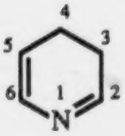


57

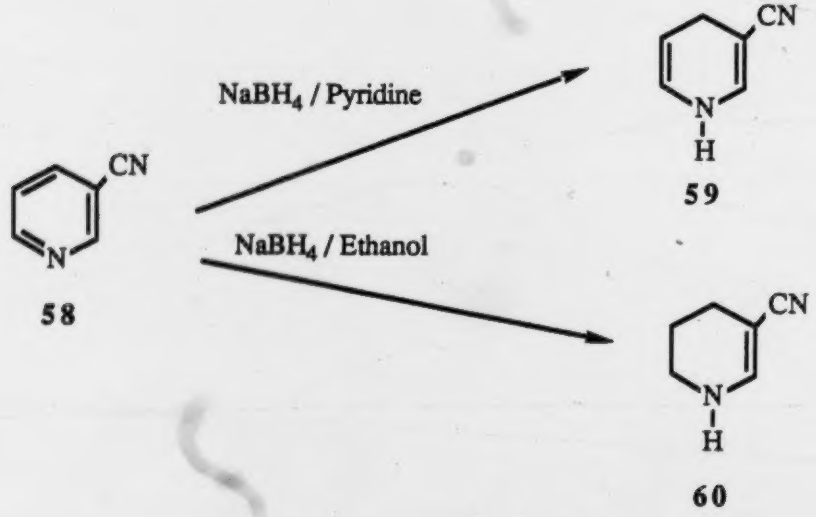
The majority of dihydropyridines investigated are 1,2-, (1,6) and 1,4-, derivatives. 1,4-Dihydropyridines are thermodynamically more stable than the 1,2- (1,6-) isomers.[196] Electron-withdrawing substituents, especially those capable of resonance interaction, such as COR, CO_2R, CN and NO_2, at the 3 and/or 5 positions stabilize the dihydropyridine ring system. Electron donating groups induce a destabilizing effect.[193]

1.3.1.0.0.0. The Synthesis of Dihydropyridines.

1,2-Dihydropyridines are commonly prepared from pyridines, whereas 1,4-dihydropyridines are synthesized mainly from cyclocondensation reactions.[179]

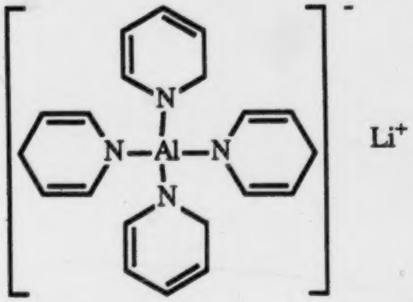
1.3.1.1.0.0. Synthesis of dihydropyridines by hydride reduction of pyridines and pyridinium salts.

The reduction of pyridines and pyridinium salts by complex metal hydrides has been reviewed.[197,198] Sodium borohydride ($NaBH_4$), the most commonly employed complex metal hydride in these reductions, reduces pyridines with electron-withdrawing substituents at the 3 or 5 position to give mixtures of 1,2- and 1,4-dihydropyridines.[199] The use of aprotic solvents prevents further reduction to the tetrahydropyridines.[200] For example $NaBH_4$ reduced 3-cyanopyridine (**58**) to the 1,4-dihydropyridine (**59**) in pyridine, whereas in ethanol the tetrahydropyridine (**60**) was obtained.



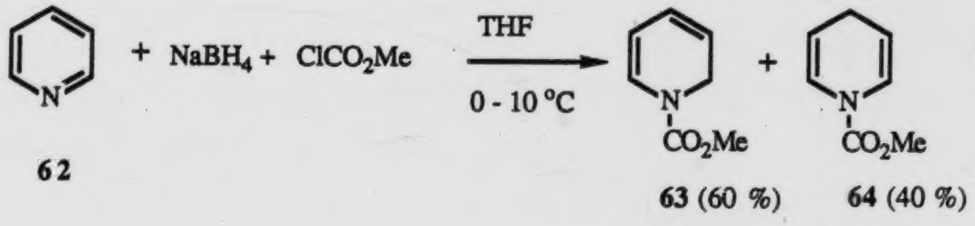
Scheme 1: Synthesis of 3-cyano-1,4-dihydropyridine and 5-cyano-1,2,3,4-tetrahydropyridine

Sodium cyanoborohydride is more selective than $NaBH_4$, affording higher ratios of 1,4- to 1,2-dihydropyridines.[199] The position of substituents such as alkyl also affects the ratio of products.[201] Lithium aluminum hydride (LAH) is more reactive and less selective, and can be used only in aprotic solvents. Lithium tetrakis(N-dihydropyridinyl)aluminate complex (**61**), a mixture of 1,2- and 1,4-dihydropyridines, is produced in aged pyridine solutions of LAH.[202]



61

Sodium borohydride reduction of pyridinium salts can yield 1,2-, 1,4- and/or 1,6-dihydropyridines. The tendency for further reduction can be minimized by use of aprotic solvents or aqueous solvents at high pH where protonation of the enamine system is less likely.[198] Bulky substituents attached to the ring nitrogen direct hydride attack to the 4-position.[203] Fowler[204] developed a widely used pyridinium salt reduction. This involves quaternization of the pyridine nitrogen with a chloroformate and reduction of the resulting pyridinium salt with $NaBH_4$ in a one pot reaction (Eq. 1).

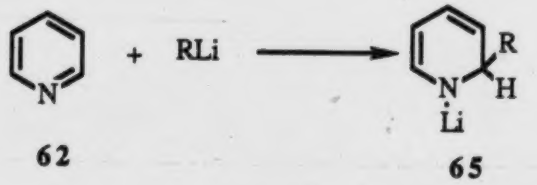


Eq. 1

Knaus and Redda [205] reacted benzenesulfonylchloride with pyridine in the presence of NaBH$_4$ at 25 °C to obtain a mixture of 1,2- and 1,4-dihydropyridines, in the ratio of 4 : 5. Lowering the temperature of the reaction afforded predominantly the 1,2-isomer, giving a ratio of 8 : 1. Reduction of pyridinium salts with sodium dithionite[206] or a copper hydride complex reagent ,[207] yields 1,4-products. Sodium borohydride also reduces *N*-alkylpyridinium salts to the dihydropyridines under strongly alkaline conditions.[208]

1.3.1.2.0.0. Nucleophilic addition of organometallic reagents to pyridines and pyridinium salts

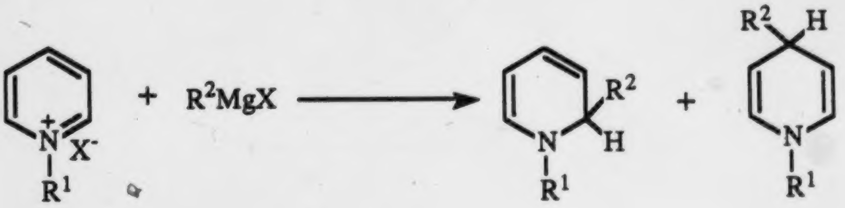
Pyridines react with alkyl- and aryllithium reagents to produce 2-substituted-1-lithio-1,2-dihydropyridines (**65**), thereby providing a convenient route to both *N*-substituted and *N*-unsubstituted-1,2-dihydropyridines.[209] (Eq..2).



Eq. 2

R = alkyl, phenyl.

Lithium organocuprates add predominately at the 4-position of pyridinium salts to give primarily 1,4-dihydropyridines.[210] Pyridines bearing electron-withdrawing substituents such as COR and CN at the 3 or 5 positions react with Grignard reagents to give 1,4- and/or 1,2-dihydropyridines.[211] In contrast to complex metal hydride give 1,4- and/or 1,2-dihydropyridines.[211] In contrast to complex metal hydride reductions, reaction takes place only at the unsubstituted positions. The addition of Grignard reagents to 1-acyl or alkylpyridinium salts (Eq. 3) has found many synthetic applications in recent years.[212,213] Alkynyl and alkenyl Grignard reagents add to N-alkoxycarbonylpyridinium salts in a highly regioselective 1,2-addition manner.[214,215] The same is true for allyltin reagents, which give 2-allylated-1,2-dihydropyridines.[216] In the presence of catalytic amounts of cuprous iodide, Grignard reagents add regiospecifically to N-acylpyridinium salts to give 1,4-dihydropyridines.[217] The general subject of nucleophilic addition to N-alkyl, N-aryl and N-acylpyridinium salts and pyridine N-oxides has been reviewed.[218,219] The addition of carbon nucleophiles to 1-alkylpyridinium salts for alkaloid syntheses has been reviewed recently.[220]



66 **67** **68**

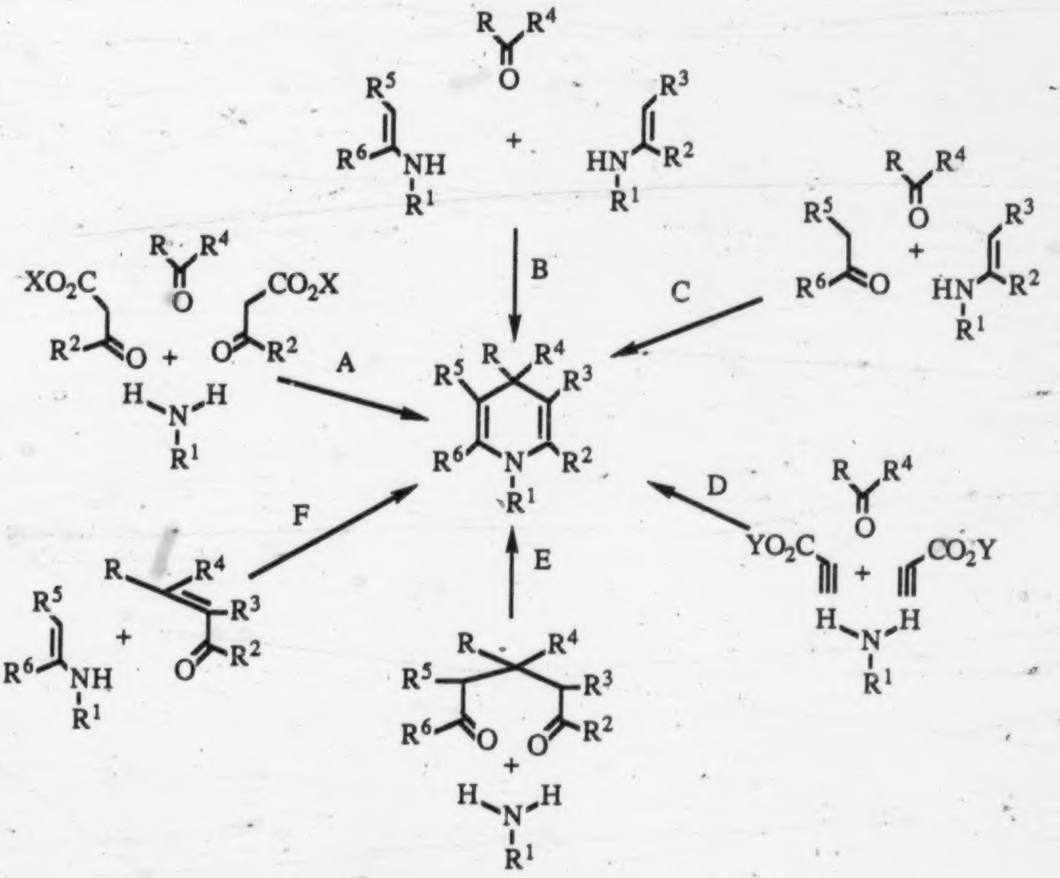
Eq. 3

R^1 = acyl, alkyl R^2 = alkyl, aryl X = Cl, Br, I

1.3.1.3.0.0. Synthesis of 1,4-dihydropyridines by cyclocondensation reactions

The Hantzsch synthesis[221] and related cyclocondensations are the most useful methods for synthesizing 4-aryl-1,4-dihydropyridine calcium channel antagonists.[222] A review on the recent synthesis of 1,4-dihydropyridines by cyclocondensation methods is available.[223] The classical Hantzsch synthesis involves the one-pot condensation of an aldehyde with a β-ketoester (acetoacetate) in a 1:2 molar ratio and ammonia (path A in

Scheme 2). This and subsequently developed cyclocondensations, which allow flexibility in the substitution pattern, are illustrated in Scheme 2.

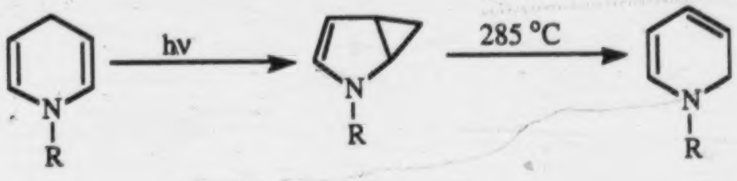

A
B
C
D
E
F
R
R^1
R^2
R^3
R^4
R^5
R^6
XO_2C
CO_2X
YO_2C
CO_2Y
NH
HN
N
H
O

Scheme 2: Synthesis of 1,4-dihydropyridines by cyclocondensation reactions

Cyclocondensation of malondialdehyde, and amino acid esters to 1,4-dihydropyridines has also been reported recently.[224]

1.3.1.4.0.0. Other methods of dihydropyridine synthesis

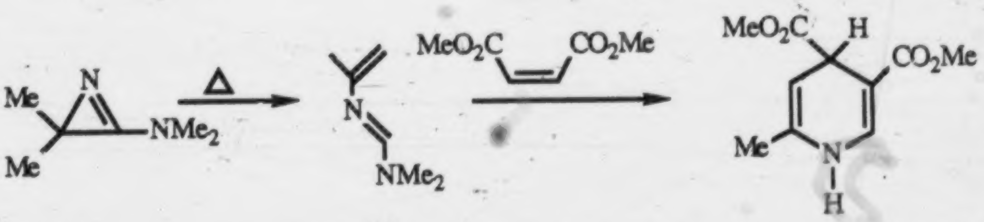
1,2-Dihydropyridines can be prepared by photochemical and thermal rearrangement of 1,4-dihydropyridines (**71** from **69** via **70**).[225] Tietze *et al* [226] have also reported the photochemical preparation of dihydropyridines. An unequivocal synthesis of N-substituted 1,4-dihydropyridines by a lengthy reaction scheme involving 1,3-dipolar cycloaddition reaction of sulfonyl azides has been reported.[227]



69 **70** **71**

Scheme 3: Synthesis of 1,2-dihydropyridines from 1,4-dihydropyridines.

Thermolysis of the 2-dimethylamino-azirine (**72**) gives 1-dimethylamino-2-azadiene (**73**) which undergoes a facile cycloaddition with electron deficient alkenes to yield the 1,4-dihydropyridine (**74**).[228]

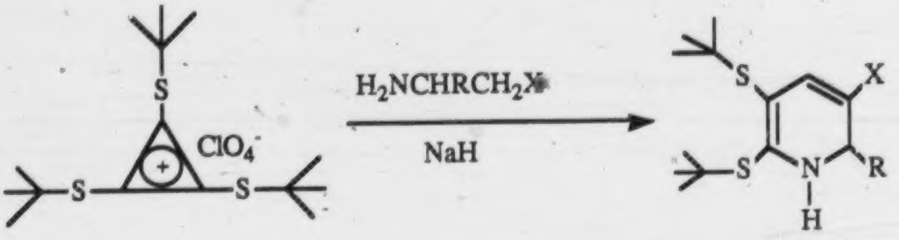


72 **73** **74**

Scheme 4: Synthesis of a 1,4-dihydropyridine by a Diels-Alder reaction.

It has recently been reported that tris(*tert*-butylthio)cyclopropenium perchlorate (**75**) reacts with β- amino acid derivatives or β-aminonitriles under basic conditions to give 1,2-

dihydropyridines (**76**).[229] 2-Substituted-1,2-dihydropyridines have also been synthesized from 2-substituted piperidines.[230]



75 **76**

Eq. 4

R = H, Me, Ph.

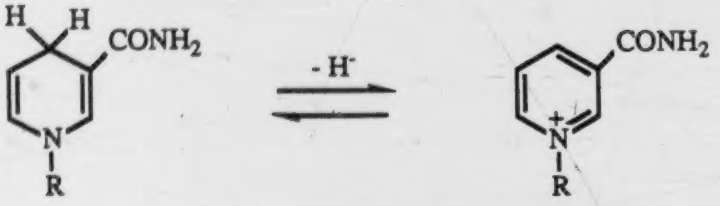
X = CN, CO_2Me

1.3.2.0.0.0. Reactions of 1,2- and 1,4-Dihydropyridines

The reactions of dihydropyridines have been extensively reviewed.[179,193,194] A recent review on the reactions of 1,4-dihydropyridines is also available.[231]

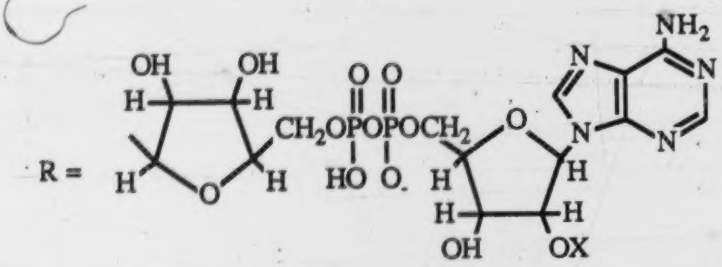
1.3.2.1.0.0. Oxidation

Dihydropyridines have a high tendency to aromatize. The dehydrogenation of 1,2- and 1,4-dihydropyridines to pyridines can be effected using numerous oxidizing agents,[193,231] which include *o*-chloranil, sulfur, potassium permanganate, dilute nitric acid and oxygen. The best example of the hydrogen transfer oxidation of dihydropyridines is provided by the biological redox couple NAD(P)H/NAD(P)$^+$ (Eq. 5). Recent reviews on NADH and its model systems have been published.[232, 233]



Eq. 5

77 **78**

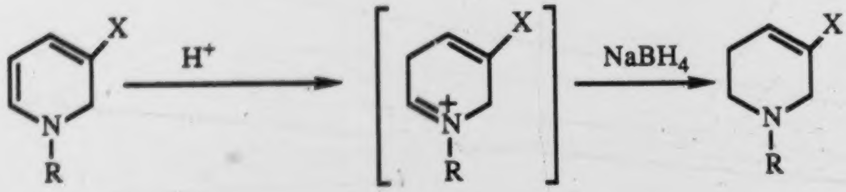


NADH, $X = H$

NADPH, $X = OPO_2H$

1.3.2.2.0.0. Reduction

Catalytic hydrogenation of dihydropyridines yields the corresponding tetrahydropyridine or piperidine derivatives.[193] This reaction has been used to distinguish 1,2- from 1,4-dihydropyridines.[234] 1,2-Dihydropyridines take up one mole of hydrogen to give tetrahydropyridines, whereas 1,4-dihydropyridines are reduced slowly to piperidines. Sodium borohydride reduction of dihydropyridines to tetrahydropyridines occurs in protic or acidic media.[198] 1,2-Dihydropyridines are more susceptible to this reaction than the 1,4- and 1,6- isomers.



Eq. 6

79 **80** **81**

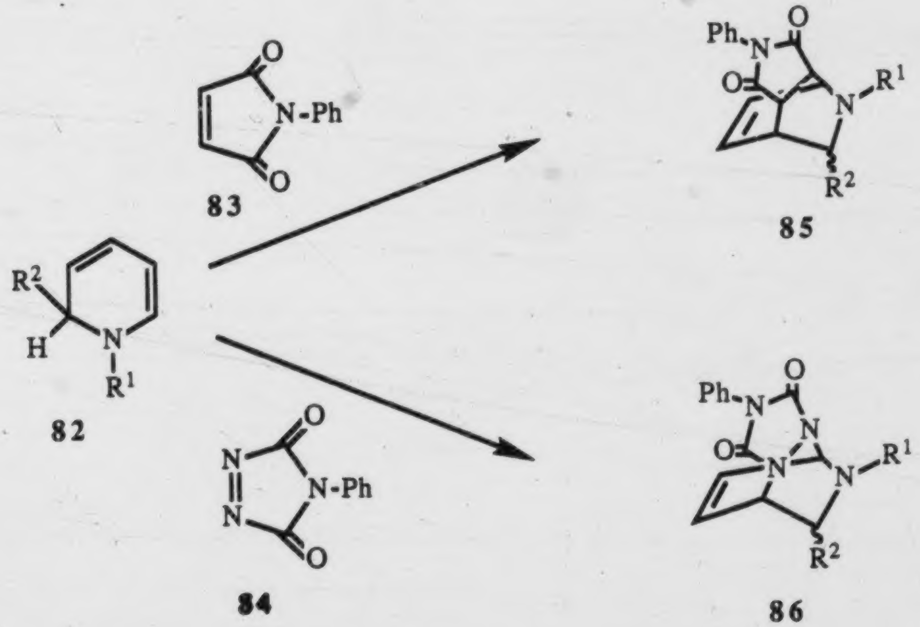
X = CN, COR.

1.3.2.3.0.0. Cycloaddition reactions .

Cycloaddition reactions of reduced pyridines have been reviewed by Sliwa.[235]

1.3.2.3.1.0. Diels-Alder reactions.

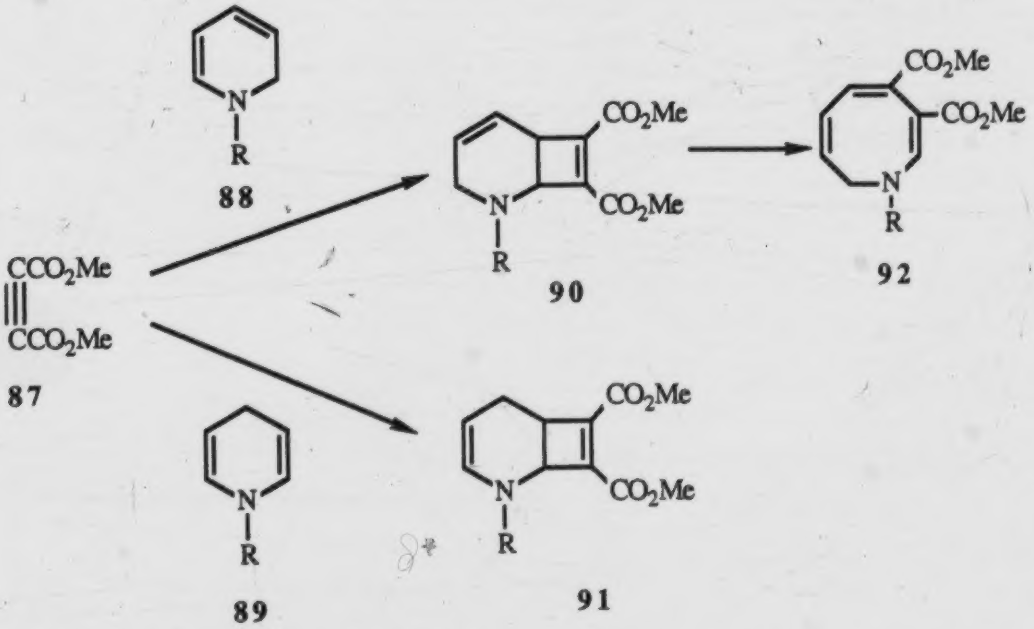
1,2-Dihydropyridines are useful dienes for both intermolecular[193,194,236] and intramolecular [237-239] Diels-Alder reactions. Knaus *et al* [240-242] and Krow *et al* [243-245] have shown that N-substituted-1,2-dihydropyridines react with maleimides (**83**) and 4-phenyl-1,2,4-triazoline-3,5-dione (**84**) to afford Diels-Alder adducts **85** and **86** respectively. The Diels-Alder reactions of 1,2-dihydropyridines with a variety of monosubstituted alkenes have been summarized.[246] Diels-Alder reactions of dihydropyridines are also included in Fowler's review of the reactivity of reduced pyridines.[247]



Scheme 5: Diels-Alder reactions of 1,2-dihydropyridines.

1.3..2.3.2.0. [2 + 2] Cycloaddition reactions

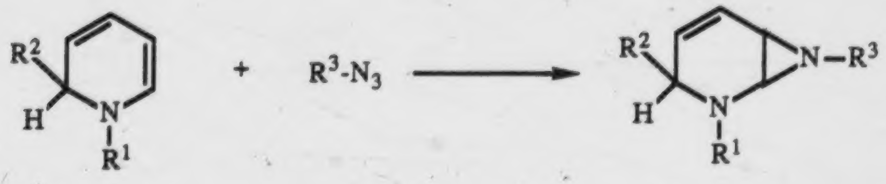
1,2- And 1,4- dihydropyridines undergo 2 + 2 cycloadditions. The 2 + 2 cycloadducts of 1,2-dihydropyridines are prone to ring expansion [248] (**90** to **92**), whereas the corresponding adducts (**91**) of 1,4-dihydropyridines are not.[249, 250]


88
N
R
CO2Me
CO2Me
N
R
90
CO2Me
CO2Me
N
R
92
CCO2Me
CCO2Me
87
89
N
R
CO2Me
CO2Me
N
R
91

Scheme 6: 2 + 2 Cycloaddition of dihydropyridines.

1.3.2.3.3.0. 1,3-Dipolar cycloaddition reactions

The olefinic bonds of 1,2-and 1,4-dihydropyridines serve as dipolarophiles for 1,3-dipolar cycloaddition reaction with organic azides[251-253] (Eq. 7). 1,2-Dihydropyridines have also been reported to undergo intramolecular nitrile oxide cycloaddition reactions.[254]



93 **94**

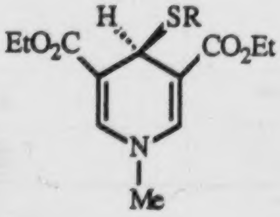
R^1 = H, alkyl. R^3 = CN, SO_2Ar, SO_2Me.

R^2 = H, alkyl, phenyl.

Eq.7

1.3.2.3.4.0. Other reactions

Dihydropyridines undergo many other reactions[179,193,194] including metallations,[255, 256] N-alkylations, rearrangements, [257] dimerizations, [258] photochemical reactions, ring opening[247] and ring transformations.[259] Thio-substituted-1,4-dihydropyridines (**95**) can also act as thiolate transfer reagents.[260] 1,2-Dihydropyridines also react photochemically with enolsilanes and oxygen to produce 3-hydroxy-1,2,3,6-tetrahydropyridines.[261]

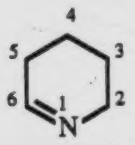


95

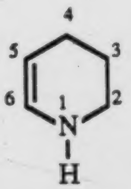
R = alkyl, aryl.

1.4.0.0.0.0. THE CHEMISTRY OF TETRAHYDROPYRIDINES

The chemistry of tetrahydropyridines has been the subject of two reviews [262,184] Tetrahydropyridines are generally more stable than dihydropyridines. Three isomeric tetrahydropyridines are theoretically possible viz, 2,3,4,5-tetrahydropyridine, (**96**,1-piperideine), 1,2,3,4-tetrahydropyridine (**97**, 2-piperideine) and 1,2,3,6-tetrahydropyridine (**98**, 3-piperideine). 1,2,3,6-Tetrahydropyridine is the only isomer prepared to date as a stable free base. The other isomers have been reported as derivatives thereof. The literature of tetrahydropyridines is to a very large extent that of 1,2,3,6-tetrahydropyridines.



96



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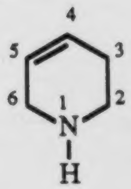


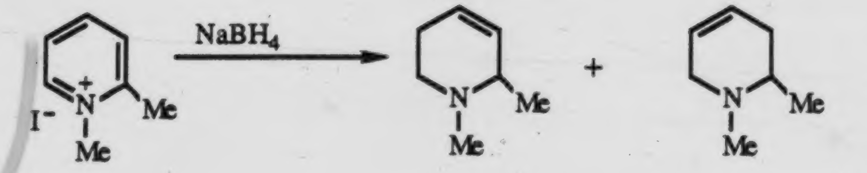
98

1.4.1.0.0.0. Synthesis of Tetrahydropyridines

The synthesis of 1,2,3,6-tetrahydropyridines has been reviewed.[261,262] The synthesis of MPTP (**50**) and structurally related compounds has also been reviewed.[191]

1.4.1.1.0.0. Reduction of pyridines and pyridinium salts.

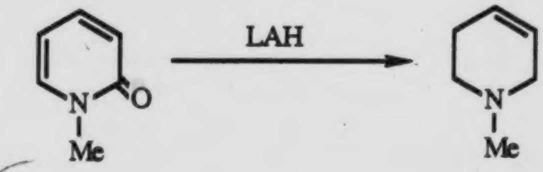
1,2,3,6-Tetrahydropyridines not substituted at nitrogen can be prepared from the corresponding pyridine compounds by reduction with aluminium hydride.[263,264] 1-Alkyl-1,2,3,6-tetrahydropyridines can be synthesized by reduction of 1-alkylpyridinium salts with formic acid (Luke's reduction)[264,265] or with complex hydrides (potassium or sodium borohydride)[197,198,266,267] in alcoholic or aqueous media (Eq. 8).



99 **100** (13 %) **101** (84 %)

Eq. 8

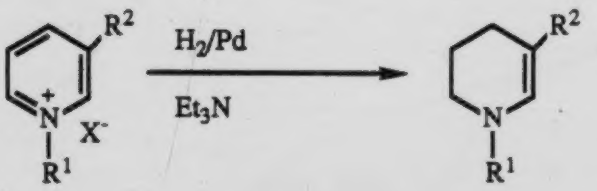
1-Methyl-1,2,3,6-tetrahydropyridines can be prepared from 1-methyl-2-pyridones by reduction with LAH or a 1:1 mixture of LAH and aluminum chloride (Eq. 9).[268]



102 **103**

Eq. 9

Partial catalytic hydrogenation of pyridinium iodides also yields tetrahydropyridines.[269] Palladium induced hydrogenation of pyridinium salts in the presence of triethylamine yields 1,2,3,4-tetrahydropyridines (Eq.10).[270] The hydrogenation of 3-acetylpyridine and related compounds to 1,2,3,4-tetrahydropyridines has also been reported.[271] Partial reduction of a 1,2-dihydropyridine to 1,2,3,6-tetrahydropyridine was accomplished with aqueous sodium borohydride in the presence of trimethylborate.[198]



R^1 = acyl

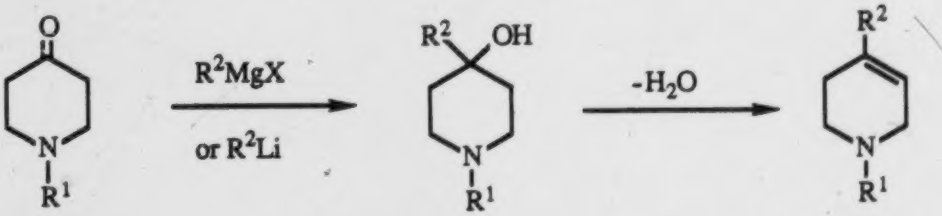
R^2 = alkyl

Eq. 10

104 **105**

1.4.1.2.0.0. From piperidones

Many tetrahydropyridine syntheses convert piperidones (**106**) to piperidinols (**107**) which can then be dehydrated to the tetrahydropyridines (**108**).[272-274]

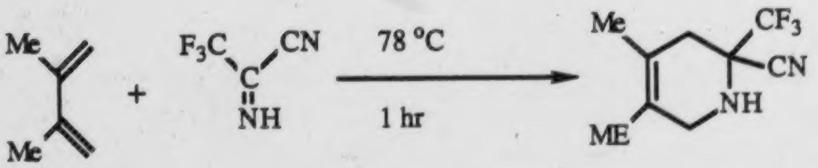

R^{2}MgX
or R^{2}Li
-H$_2$O
O
N
R^1
R^2
OH

106 **107** **108**

Scheme 7: Synthesis of 1,2,3,6-tetrahydropyridines from piperidones.

1.4.1.3.0.0. From Diels-Alder reactions

Many 1,2,3,6-tetrahydropyridines have also been synthesized by the reaction of imine dienophiles with dienes[275-278] as illustrated below (Eq.11).

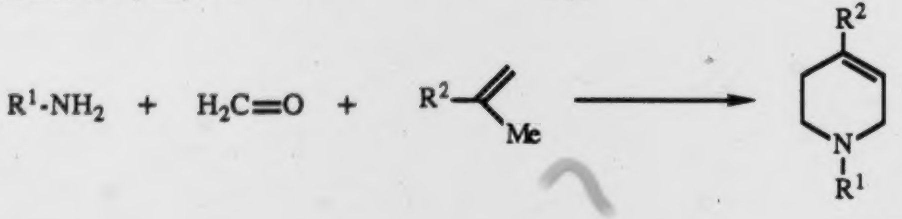

Me
Me
+
F$_3$C
CN
C
NH
78 °C
1 hr
Me
ME
CF$_3$
CN
NH

109

Eq. 11

1.4.1.4.0.0. Cyclocondensation methods

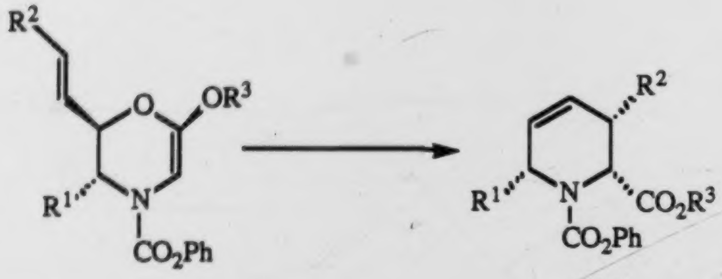
The condensation of an activated alkene (e.g. alpha-methylstyrene), formaldehyde and an amine is a useful industrial method for the synthesis of 1,2,3,6-tetrahydropyridine derivatives (**110**).[279]


R^1-NH_2 + $H_2C{=}O$ +
R^2
Me
R^2
N
R^1

Eq. 12

110

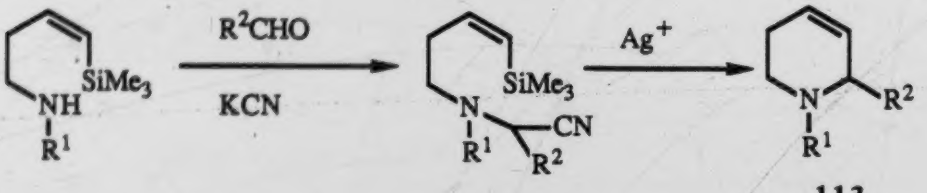
The stereo-controlled synthesis of tetrahydropyridines (**112**), which involves a ketene-acetal Claisen [3,3] sigmatropic rearrangement reaction, was recently reported.[280]


R^2
O
OR^3
R^1
N
CO_2Ph
R^2
R^1
N
CO_2R^3
CO_2Ph

111 **112**

Eq. 13

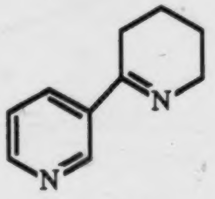
A general method has recently been described[281] for the synthesis of 1,2,3,6-tetrahydropyridines (**113**) as illustrated by Scheme 8.


$SiMe_3$
NH
R^1
R^2CHO
KCN
$SiMe_3$
N
R^1
CN
R^2
Ag^+
N
R^1
R^2

113

Scheme 8: Synthesis of 1,2,3,6-tetrahydropyridines by iminium ion-vinylsilane cyclization.

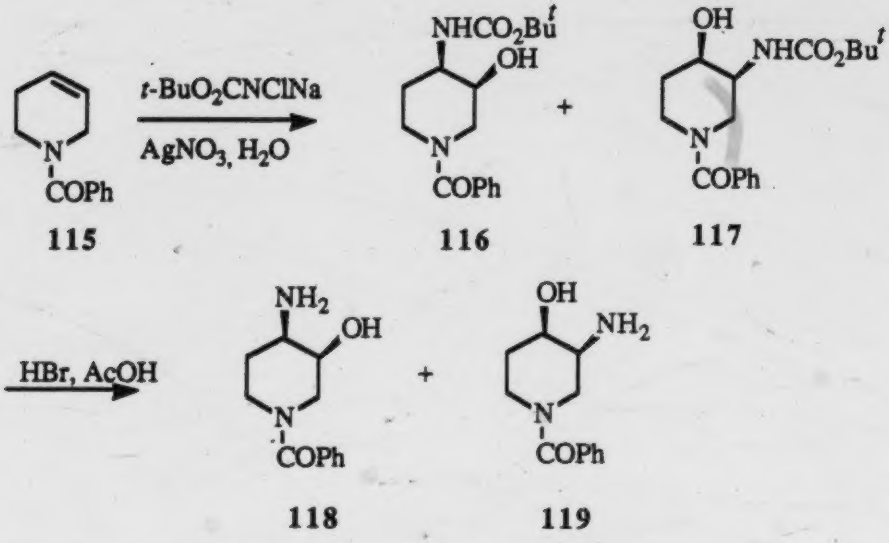
A series of substituted 1,2,3,6- and 1,2,5,6-tetrahydropyridines have been synthesized via intramolecular 1,6-Michael addition of methoxycarbonyl-2,4-dienylamines.[282] The 2,3,4,5-tetrahydropyridine **114** has been synthesized in 75% yield via the Schmidt reaction using tertiary azides.[283]



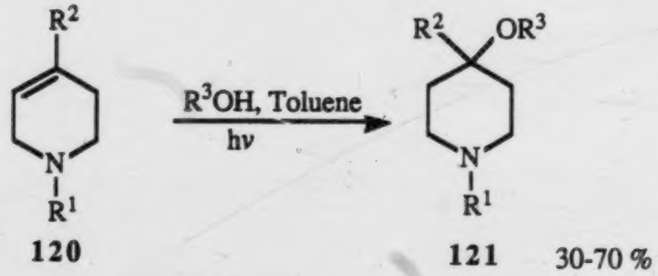
114

1.4.2.0.0.0. The Reactions of Tetrahydropyridines

These reactions are mainly those involving the olefinic bond and the nitrogen centre. The olefinic bond of 1,2,3,6-tetrahydropyridine undergoes addition reactions similar to those of alkenes. Thus 1,2,3,6-tetrahydropyridines undergo catalytic hydrogenation to afford piperidines.[284] Bromination, epoxidation, hydroxylation and hydroboration reactions have been reported.[262] The stereospecific vicinal *cis*-oxyamination of N-substituted-1,2,3,6-tetrahydropyridine has also been achieved (Scheme 9).[285] The photoaddition of alcohols to 1,2,3,6-tetrahydropyridines (Eq. 14) has also been reported recently.[286]


t-BuO2CNClNa
AgNO3, H2O
HBr, AcOH
115
116
117
118
119

Scheme 9: Oxyamination of N-acyl-1,2,3,6-tetrahydropyridine.

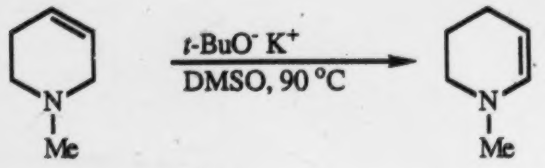

R3OH, Toluene
hν
120
121
30-70 %

Eq. 14

R^1 = H, alkyl R^3 = alkyl

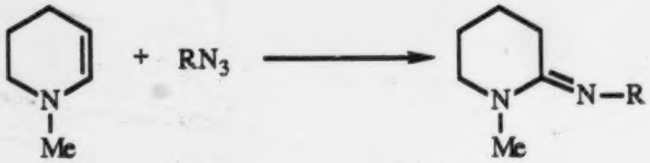
R^2 = alkyl, indyl

Isomerization of 1-methyl-1,2,3,6-tetrahydropyridine (**103**) to 1-methyl-1,2,3,4-tetrahydropyridine (**122**) has been developed as a useful synthetic method (Eq. 15).[287] Isomerization of 1-acyl-1,2,3,6-tetrahydropyridines to the 1,2,3,4-isomers using rhodium complex hydrides[287] and more recently palladium on carbon[289] has also been reported. 1,2,3,4-Tetrahydropyridines are enamines, and undergo reactions characteristic of the latter. Thus 1-methyl-1,2,3,4-tetrahydropyridine (**122**) is a good dipolarophile for 1,3-dipolar cycloaddition reactions with organic azides (Eq. 16).[290]


N
Me
t-BuO⁻ K⁺
DMSO, 90 °C
N
Me

103 **122**

Eq. 15


N
Me
+ RN₃
N
N—R
Me

122 **123** R = CN, SO_2Ph, etc.

Eq. 16

2.0.0.0.0.0. OBJECTIVES OF RESEARCH

Tolerance, physical dependence and a high incidence of abuse are serious problems associated with the use of currently available opioid analgesics. Consequently, there is an urgent need for analgesics which are devoid of these disadvantages, for the management of severe pain. The discovery of multiple opioid receptors that possess different pharmacological profiles offers an opportunity to design selective ligands that lack effects exhibited by morphine and other opioids in clinical use.[133]

A class of novel potent piperidylidene-2-sulfonamide analgesics was discovered recently in this research group.[291] The most potent compound, 1-[2-(4-nitrophenyl) ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide, was 10,000 fold more potent than morphine sulfate in mice. The analgesic activity was blocked by naloxone, indicating that the piperidylidenesulfonamides interact with opioid μ-receptors.

The primary objective of the present research was to acquire additional analgesic structure-activity relationships (SARs) for this piperidylidenesulfonamide class of compounds. It was of interest to synthesize and pharmacologically evaluate the antinociceptive (analgesic) activity of new tetrahydropyridylidene- and piperidylidene-2-sulfonamide analogs. An oxygen spacer between the aromatic group and the sulfonyl moiety was investigated to test the hypothesis[291] that the sulfonyl sulfur atom was a bioisostere of the quaternary carbon atom present in clinical opioids such as meperidine. Substituents at C-6 were incorporated to determine the effect of such substitution on analgesic activity. Isomeric pyridyl analogs would also provide information on the effect of the pyridine ring nitrogen position on analgesic activity. Dihydropyridine analogs were also synthesized to investigate the bioisosteric relationship between the pyridine and dihydropyridine ring systems with respect to analgesic activity in this class of piperidylidenesulfonamides.

The paucity of information on pyridine analogs of opioid analgesics, and the virtual absence of any studies involving dihydropyridine analogs, provided the impetus for the latter part of this research. In view of the fact that selective biological activity can be achieved by the bioisosteric replacement of a phenyl moiety by a pyridyl ring, it was considered important to undertake the synthesis and antinociceptive evaluation of new pyridine and dihydropyridine analogs of meperidine (pethidine) and fentanyl. Meperidine is the most widely used synthetic opioid analgesic, and fentanyl is the opioid of choice for neuroleptanalgesia.

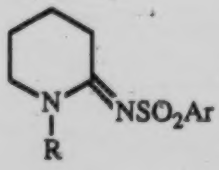
3.0.0.0.0.0. RESULTS AND DISCUSSION

3.1.0.0.0.0. DRUG DESIGN CONSIDERATIONS

The search for a non-addictive analgesic agent suitable for the management of severe pain was initiated following the discovery that morphine possessed addictive properties. To date, no non-addictive major opiate agonist has been developed. The discovery of multiple opioid receptors and advances made in the investigation of their different pharmacological profiles has made it possible to dissociate undesirable side effects such as respiratory depression,[293] tolerance and physical dependence[294] from analgesia. The recently proposed μ_1-receptor [293] is believed to mediate analgesia, but not respiratory depression or withdrawal symptoms.[293,295] The design of selective agonist ligands for the μ_1-receptor, which binds to most opioids with similar affinity[133] would constitute an important advance.

3.1.1.0.0.0. Novel Piperidylidene-2-sulfonamide Analgesics

Two classes of novel analgesic agents have recently been developed in this research group. A series of 1-methylpiperidylidene-2-sulfonamides (**124**) were shown to exhibit potent analgesic activity that was antagonized by either naloxone or the structurally related 1-cycloalkylalkyl piperidylidene-2-sulfonamide analogs.This antagonism indicated an interaction with an opioid μ-receptor. The 1-cycloalkylalkyl analogs (**124**, R = cycloalkylalkyl) displayed μ-receptor-antagonist and κ-receptor agonist activity since their analgesic activity was blocked by the κ-receptor antagonist MR-2266.



124

Ar = Ph, C_6H_4-4-Cl, C_6H_4-2-NO_2, C_6H_4-3-NO_2, etc.

R = Me, CH_2CH_2Ph, CH_2–◁, CH_2–◇, etc.

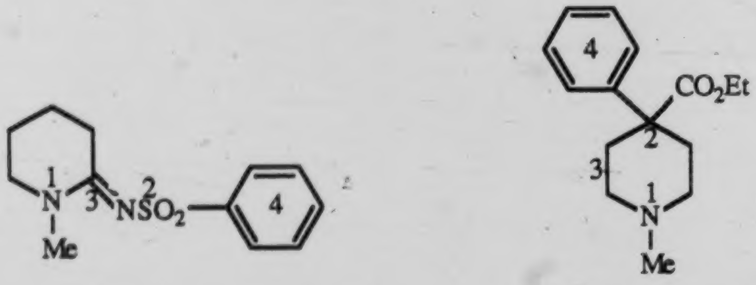
It has therefore been hypothesized that 1-substituted-piperidylidene-2-arylsulfonamides can interact with opioid receptors in a manner similar to morphine, methadone meperidine or other opioid analgesics in clinical use based upon the following molecular structural similarities (Fig. 2):

1) A tertiary (3^{O}) amino group is present.

2) The sulfonyl moiety is a bioisostere for the quaternary carbon present in meperidine and related compounds.

3) The C=N moiety is equivalent to the two carbon chain separating the 3^{O}-amino nitrogen and the quaternary carbon atom present in meperidine and related compounds.

4) A phenyl moiety (Ar) attached directly to the sulfonyl sulfur atom is present.



124

Meperidine (**11a**)

Fig.2: Structural comparison of 1-methylpiperidylidene-2-benzenesulfonamide (**124**) and meperidine.

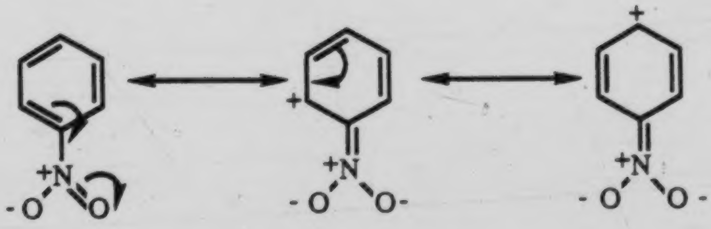
Preliminary SARs revealed that an aromatic ring was required for maximum analgesic activity of 1-substituted-piperidylidene-2-sulfonamides.[291] Application of a manual technique used in drug design reported by Topliss[296] to determine the effect of changes in physicochemical parameters such as hydrophobic (π) and electronic (σ)

substituent effects upon analgesic activity of the piperidylidene-2-sulfonamides did not reveal any correlation between these parameters and analgesic activity.[291]

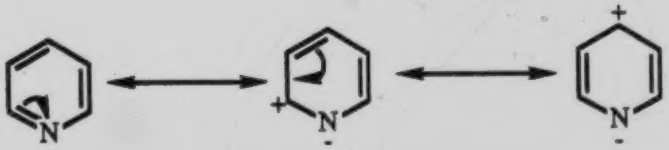
3.1.2.0.0.0. Pyridine and Benzene Bioisosterism

Bioisosteres are broadly defined as "groups or molecules which have chemical and physical similarities producing broadly similar biological properties".[297] The medicinal chemistry literature is replete with examples illustrating the concept of bioisosterism. The subject of bioisosterism in drug design has been reviewed recently.[298]

Pyridine and benzene are classical isosteres according to the definition by Burger [299] and Korolkovas.[300] However, the presence of the nitrogen heteroatom in pyridine confers physicochemical properties to the pyridine ring which are different from those of the benzene ring. For example, pyridine is basic and hydrophilic,whereas benzene is neutral and hydrophobic.[301] The charge distribution of the pyridine ring is similar to that of a benzene ring with an electron withdrawing substituent such as a nitro (NO_2) group[302] (Fig. 3). Based on the electron distribution pattern of the pyridine ring, pyridodiazepines were designed and shown to exhibit anticonvulsant activity similar to the benzodiazepines in clinical use.[303]



Resonance structures of nitrobenzene



Resonance structures of pyridine

Fig. 3: Similarities between the charge distribution for pyridine and nitrobenzene rings.

The pyridine nitrogen lone-electron pair can induce a steric effect as shown by the relative potency order observed for 4-(pyridyl) analogs of calcium channel antagonists. For example, 4-(2-, 3- and 4-pyridyl)-1,4-dihydropyridine nifedipine analogs were bioisosteric with the respective 4-(2-,3-, and 4-nitrophenyl) analogs.[304] The difference in pharmacological activity of isomeric pyridine compounds is well documented. In a series of novel isomeric pyridine heterocyclic histamine H_2-receptor antagonists, the relative potency order was 2-pyridyl > 4-pyridyl > 3-pyridyl.[305] In an isomeric series of pyridylethylphenols evaluated as cyclooxygenase and lipooxygenase inhibitors, the 2- and 3-pyridyl isomers were active, whereas the 4-pyridyl isomer was inactive.[306]

In some instances pyridyl derivatives have been reported to exhibit superior pharmacological profiles and selectivity to the corresponding phenyl analogs. In a recent study[307] involving tetrahydroisoquinolinone cardiotonic agents, where bioisosteric relationship between pyridyl and phenyl rings was investigated, it was concluded that pyridyl substituents were more appropriate for positive inotropic activity than a phenyl substituent. In a study investigating arylethylphenols as cyclooxygenase and lipoxygenase inhibitors, the pyridyl analogs exhibited more potent *in vivo* antiinflammatory and higher lipooxygenase inhibitory activity than the corresponding phenyl analogs.[306] It was therefore envisaged that opioid receptor selectivity may be achieved by replacement of the phenyl ring by a pyridyl ring in opioid analgesic agents.

3.1.2.1.0.0. Pyridine and benzene bioisosterism with respect to opioid analgesic activity

Several studies pertaining to phenyl-pyridyl bioisosterism for opioid analgesics have been reported. Hellerbach *et al* [41] replaced the phenyl ring by a 2-and 4-pyridyl ring in a class of *N*-aralkyl morphinans. The 2-pyridyl compound was eleven times more active than the phenyl derivative, whereas the 4-pyridyl analog exhibited only one-half the analgesic potency of the phenyl derivative. Elpern and co-workers showed that the *N*-[2-(4-pyridyl)ethyl]- and *N*-[2-(2-pyridyl)ethyl] analogs of meperidine were four and two times more potent than the *N*-[2-(phenyl)ethyl] analog, respectively.[308]

Beckett *et al* [309] reported that incorporation of 4-(2-pyridyl) ring in place of the 4-phenyl ring in the prodine class of compounds (reversed esters of meperidine) reduced analgesic activity. Their conclusion that isosteric replacement of a phenyl by a pyridyl ring was detrimental to analgesic activity was not substantiated since these investigators did not examine replacement by a 3- or 4-pyridyl ring. Berger and co-workers[310] also showed that replacement of the 4-phenyl substituent in a series of prodines by a 2- and 3- pyridyl rings reduced analgesic activity. Although the 3-pyridyl analog exhibited only one-half of the analgesic potency of meperidine, it was only one-half as toxic as meperidine.

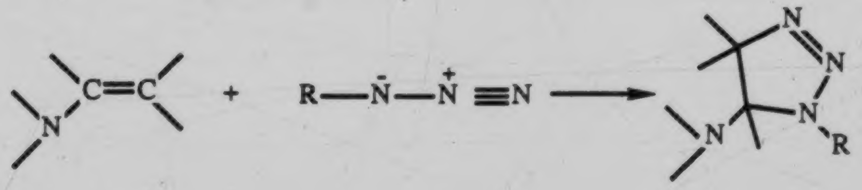
Mosher and Tessieri [311] replaced one of the phenyl substituents of methadone (**13a**) by a 3-pyridyl ring and found that activity was reduced by 70 %. The first reported systematic study investigating the effect which replacement of phenyl by all three isomeric pyridyl rings had on analgesic activity was by Hiltman *et al*.[85] For the pyridyl analogs of diampromide (**14**) these authors reported that the 2-pyridyl isomer, propiram (**15a**) was the most potent, exhibiting an activity equivalent to that of meperidine. The 3-pyridyl analog displayed lower activity,and the 4-pyridyl isomer was inactive.

Grossman and co-workers[312] also replaced the phenyl group of the anilido moiety of fentanyl (**12a**) by all three isomeric pyridyl rings. The 2-pyridyl analog exhibited the most potent activity, although it was only one-sixth as potent as the parent compound. In this series the 3-pyridyl analog was less active, whereas the 4-pyridyl isomer displayed much weaker activity. Zhu *et al* [313] reported that replacement of the 1-[2-phenylethyl]-substituent by a 1-[2-(2-pyridyl)ethyl] substituent reduced activity relative to fentanyl in the mouse hot plate analgesic test. Chagngying and Lemin [314] reported that the replacement of the phenyl substituent by pyridyl in 3-methylfentanyl series of compounds resulted in the potency profile 3-pyridyl > 4-pyridyl > 2-pyridyl. These pyridyl analogs were all less active than 3-methylfentanyl. In a recent study which investigated bioisosteric replacement of the phenyl ring of the anilido moiety of fentanyl analogs by heteroaryl groups, the 2-pyridyl substituent was found to be the most suitable, and provided the most potent compound in each group of amides tested.[80]

3.2.0.0.0.0. SYNTHESES

3.2.1.0.0.0. 1,3-Dipolar Cycloaddition Reaction of Organic Azides with Enamines

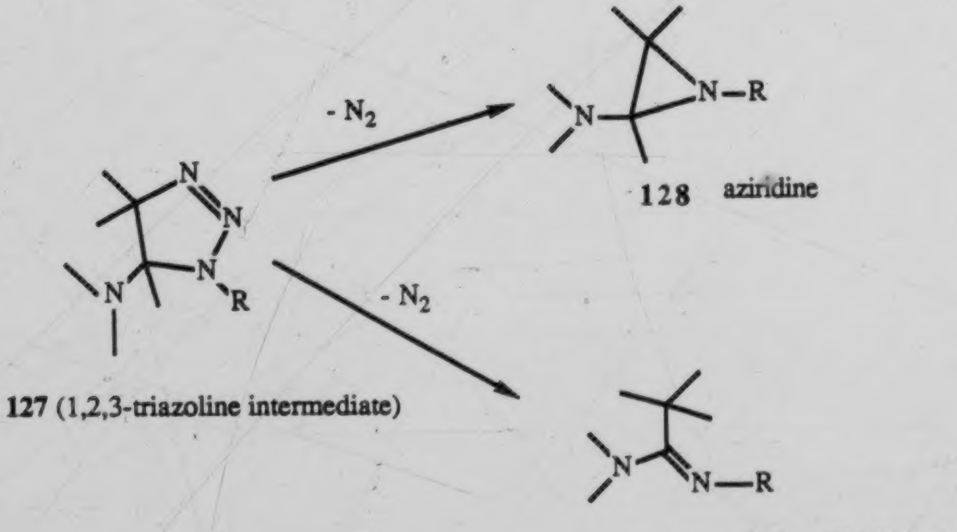
The preparation and synthetic applications of organic azides has been reviewed recently.[315] 1,3-Dipolar cycloaddition reactions were reviewed in a recent comprehensive monograph.[316] The 1,3-dipolar cycloaddition reaction rate of enamines with organic azides is faster than for any other known class of olefins (Eq. 17). The initial products are triazolines (**127**).



Eq. 17

125 **126** **127** (triazoline adduct)

The triazoline adduct is isolable in some reactions, whereas in other reactions it decomposes by elimination of nitrogen gas to afford an aziridine (**128**) or a Schiff base (**129**)[317] (Scheme 10).



127 (1,2,3-triazoline intermediate)

128 aziridine

129 imine (Shiff base)

Scheme 10: Formation of aziridines and imines from triazoline adducts.

3.2.1.1.0.0. Mechanism and selectivity

In the 1,3-dipolar cycloaddition reaction, the azide group is the 1,3-dipolar species and the enamine olefinic bond is the dipolarophile. The reaction is concerted but not synchronous.[318] It has been postulated that the reaction proceeds via a polar transition state as illustrated in Fig. 3.[319] The formation of bond "a" is more advanced than the formation of bond "b".

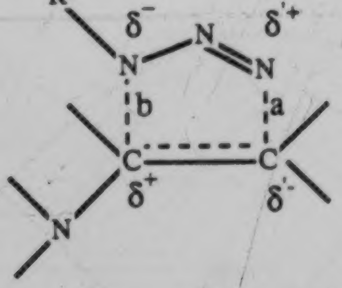
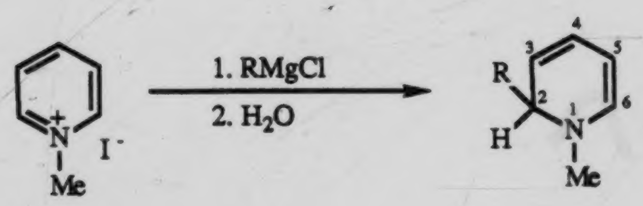


Fig. 3: Transition state for the azide enamine cycloaddition reaction.

Frontier molecular orbital (FMO) theory [320] has been used to rationalize the reactivity, regiochemical and stereochemical selectivity of cycloaddition reactions.[316] According to FMO theory, there is overlap of the highest occupied molecular orbital (HOMO) with the lowest unoccupied molecular orbital (LUMO) during bond formation. For maximum HOMO-LUMO overlap, it is essential that the HOMO terminus with the larger orbital coefficient overlaps with the LUMO terminus also possessing the larger orbital coefficient.[320] The reaction of organic azides with enamines, which are electron-rich alkenes, is a dipole LUMO controlled reaction. Orbital coefficients calculated for phenyl azide and enamines [321] show that the terminal nitrogen of the azido group and the terminal carbon of the enamine double bond have the larger orbital coefficients. Therefore, the nitrogen atom of the azido group to which the substituent is attached always adds to the carbon adjacent to the amino group of the enamine.[322] Electron-withdrawing substituents attached to the azido group accelerate the reaction rate.

3.2.2.0.0.0. Synthesis of 1-Methyl-2-alkyl(or phenyl)-1,2-dihydropyridines (131e-g).

1,2-Dihydropyridines (**131e-g**) were synthesized for use as dipolarophiles in subsequent 1,3-dipolar cycloaddition reactions. A method similar to that of Thiessen and co-workers was employed[323] (Eq. 18). The reaction of N-methylpyridinium iodide (**130**) with a Grignard reagent in dry ether at -78 ^{o}C as illustrated in equation 18 afforded **131e-g** in 73 to 84 % chemical yields (Table 2).



130

131

Eq. 18

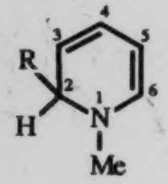
e, R = Me

f, R = *n*-Bu

g, R = Ph

This reaction was carried out at a low temperature (-78 °C) in anhydrous ether as solvent, in order to maximize the formation of the 1,2-dihydropyridine (kinetic product) relative to the 1,4-dihydropyridine (thermodynamic product) isomer. The infrared (IR) spectra (Table 2) displayed two stretching vibrations in the 1570-1640 cm^{-1} region which is characteristic for the 1,2-dihydropyridine ring system.[193,236] The ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra for compounds **131e-g** (Table 2) indicated that the relative chemical shift positions for the dihydropyridine ring protons (δ) are H-6 > H-4 > H-3 > H-5 > H-2, except for compound **131g** where the electron-withdrawing phenyl substituent deshields H-2 causing it to resonate at lower field than H-5. This relative chemical shift profile is typical for 1,2-dihydropyridines.[179, 324]

Table 2: Physical and Spectral Data for 1-Methyl-2-substituted-1,2-dihydropyridines (131e-g).



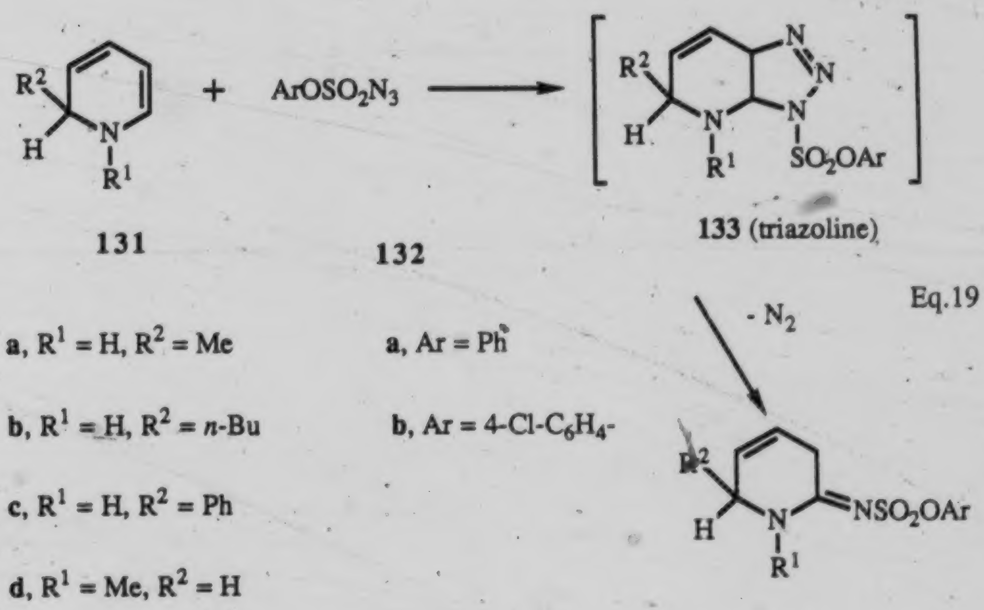
131

Entry	R	% Yield	Physical State	IR (neat), cm^{-1}	^{1}H NMR (CDCl$_3$), δ
131e	Me	73	oil	1640, 1580	1.1 (d, J = 6Hz, 3H, C-2 Me), 2.8 (s, 3H, NMe), 4.0 (m, 1H, H-2), 4.55 (d, J = 6Hz of d, J = 8.5Hz, 1H, H-5), 4.95 (d, J = 8.5Hz of d, J = 4.5Hz, 1H, H-3), 5.72-5.98 (m, 2H, H-4, H-6).
131f	*n*-Bu	80	oil	1630, 1570	0.9 (t, J = 7 Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.2-1.8 (m, 6H, $\mathit{CH_2CH_2CH_2}CH_3$), 2.8 (s, 3H, NMe), 3.95 (m, 1H, H-2), 4.55 (d, J = 6Hz of d, J = 8.5Hz of d, J = 2Hz, 1H, H-5), 4.95 (d, J = 8.5Hz

					of d, J = 4.5Hz of d, J = 2Hz, 1H, H-3), 5.88 (d, J = 8.5Hz of d, J = 8.5Hz, 1H, H-4), 5.98 (d, J = 6Hz, 1H, H-6).
131g	Ph	84	oil	1640, 1570	2.6 (s, 3H, NMe), 4.6 (d, J = 6Hz of d, J = 8.5Hz, 1H, H-5), 4.95 (d, J = 4.5Hz, 1H, H-2), 5.12 (d, J = 9Hz of d, J = 4.5Hz, 1H, H-3), 5.9-6.1 (m, 2H, H-4, H-6), 7.3-7.45 (m, 5H, phenyl hydrogens).

3.2.3.0.0.0. Synthesis of 1,2,3,6-Tetrahydropyridylidene-2-aryoxysulfonamides (134a-h)

The 1,2,3,6-tetrahydropyridylidene-2-aryloxysulfonamides (**134a-h**) were synthesized in 61-98 % chemical yields using the facile regiospecific 1,3-dipolar cycloaddition reaction[251-253] of 1,2-dihydropyridines (**131a-g**) with aryloxysulfonyl azides (**132a**, **b**, Eq. 19). The reaction proceeded rapidly at 0-25 °C, via the labile triazoline adduct **133**. Adduct **133** decomposed spontaneously by elimination of nitrogen gas to afford the tetrahydropyridylidene products **134a-h**. The rate of decomposition of the triazoline adduct was enhanced by the electron-withdrawing sulfonyl group which blocks the stabilizing resonance of the triazoline system. It has been reported that although stable triazoline adducts prepared by the reaction of ethoxycarbonyl azide with ketene S-S acetals have been isolated, attempts to isolate the corresponding N-sulfonyl triazolines failed.[325] The course of decomposition of the 1,2,3-triazoline intermediate is reported to depend on the stereochemistry of the substituents on the C-C bond of the triazoline ring. Cyclopentene, cycloheptene and *cis*-cyclooctene reacted with phenyl azide at 40-90 °C to give imine products, whereas cyclohexene and *trans*-cyclooctene yielded only aziridine products.[326]


R2
H
N
R1
+
ArOSO2N3
N
N
N
SO2OAr
- N2
NSO2OAr

131 **132** **133** (triazoline) **134**

Eq.19

a, R^1 = H, R^2 = Me

b, R^1 = H, R^2 = *n*-Bu

c, R^1 = H, R^2 = Ph

d, R^1 = Me, R^2 = H

e, R^1 = R^2 = Me

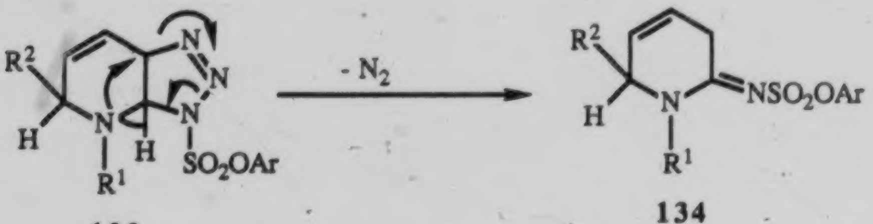
f, R^1 = Me, R^2 = *n*-Bu

g, R^1 = Me, R^2 = Ph

a, Ar = Ph

b, Ar = 4-Cl-C_6H_4-

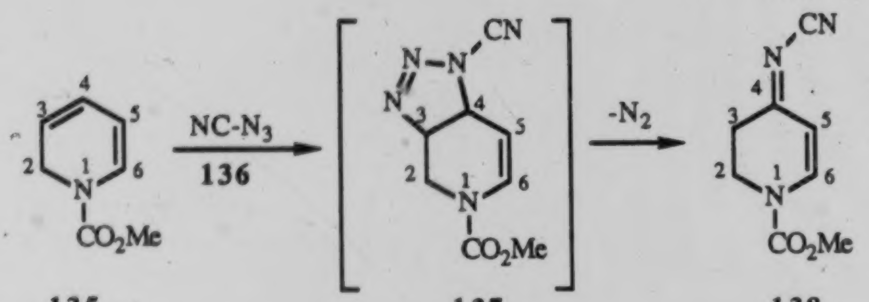
A plausible mechanism by which elimination of nitrogen from the triazoline intermediates **133** occurs to form the imines **134** is illustrated below . This mechanism involves a concerted fragmentation with a 1,2-hydride shift. McManus *et al* [327] have observed 1,2-alkyl shifts during the decomposition of 1,2,3-triazolines.



133

134

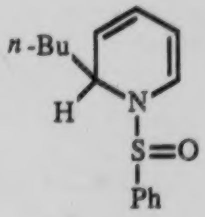
Other mechanisms have also been suggested for the decomposition of triazolines to imines.[327, 328] The electron density of the dienamine olefinic bond is a primary determinant which directs the regiochemistry of the 1,3-dipolar cycloaddition reaction. The olefinic bond possessing the higher electron-density is more reactive. For example reaction of N-acyl-1,2-dihydropyridines with organic azides results in addition to the 3,4-olefinic bond (Eq. 20)[329] in contrast to addition to the more reactive 5,6-olefinic bond when N-methyl-1,2-dihydropyridines such as **131** are employed. The 1-carbonyl substituent present in **135** deactivates the 5,6-olefinic bond since the nitrogen lone-electron pair is preferentially delocalized across the amide moiety rather than the 5,6-enamide moiety. This is clearly illustrated by the fact that the ^1H NMR spectra of 1-acyl-1,2-dihydropyridines often show the presence of two rotational isomers due to restricted rotation about the amide nitrogen-to-carbonyl bond. The regiospecific 1,3-dipolar cycloaddition reaction of **135** with organic azides therefore takes place at the more reactive 3,4-olefinic bond.



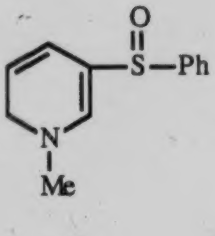
135 **137** **138**

Eq. 20

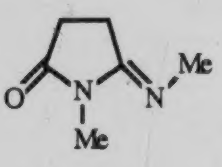
The reaction of 2-*n*-butyl-1,2-dihydropyridine **131b** with phenylsulfinyl azide [PhS(O)N$_3$]^{330} afforded 1-phenylsulfinyl-2-*n*-butyl-1,2-dihydropyridine (**139**, 40%) rather than the expected 1,3-dipolar cycloaddition reaction product. A similar reaction with 1-methyl-1,2-dihydropyridine (**131d**) yielded 1-methyl-5-phenylsulfinyl-1,2-dihydropyridine (**140**, 50 %). These results indicate that phenylsulfinyl azide acts as an electrophilic reagent,^{323} rather than a 1,3-dipole, upon reaction with cyclic dienamines such as **131b** and **d.**



139



140

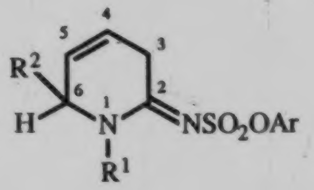


141

The IR spectra of compounds **134a-h** (Table 3) were consistent with their assigned structures. Compounds **134a**, **b** and **c** displayed NH stretching absorption bands at 3260 , 3230 and 3221 cm^{-1}, respectively. Absorption bands in the 1614-1630 cm^{-1} and 1570-1598 cm^{-1} ranges indicated the C=C and C=N bonds , respectively.The low C=N absorption frequency is attributed to delocalization of the C=N bond due to conjugation with the sulfonyl group. This conjugation imparts some single bond character to the C=N bond. A similar effect on the IR absorption frequency of the C=N bond through conjugation has been observed.[331,332]

The ^{1}H NMR chemical shift data for compounds **134a-h** were also consistent with the assigned structures (Table 3). Compound **134a** exhibited a doublet at δ 1.2 (J = 7Hz) for the C-6 methyl group, a multiplet at δ 3.16 for H-3, a multiplet at δ 4.16 for H-6, a complex multiplet at δ 5.8 for the olefinic H-4 and H-5 protons, a multiplet at δ 7.4 for the phenyl protons and a broad singlet at δ 8.44 for the NH, which exchanged with deuterium oxide (D_2O). The ^{13}C NMR spectrum of compound **134b** exhibited a chemical shift at δ 163.56 in deuterochloroform ($CDCl_3$) which indicated the presence of the C=N bond. A similar ^{13}C NMR chemical shift (δ 163.56) was reported for the C=N carbon of the 1-methyl-5-oxopyrrolidylidene **141**.[331] The physical and microanalytical data for **134a-h** are summarized in Table 6. The low resolution mass spectrum for compound **134g** showed the major fragments presented in Fig. 5.

Table 3: IR and NMR Spectral Data for 1,2,3,6-Tetrahydropyridylidene-2-aryloxysulfonamides (**134 a-h**).



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Entry	R^1	R^2	Ar	IR (KBr), cm^{-1}	NMR (CDCl$_3$), δ
134a	H	Me	Ph	3260 (NH), 1625 (C=C), 1600 (C=N).	^{1}H: 1.2 (d, J = 7Hz, 3H, C-6 Me), 3.16 (m, 2H, H-3), 4.16 (m, 1H, H-6), 5.8 (m, 2H, H-4, H-5), 7.4 (m, 5H, phenyl hydrogens), 8.44 (br s, 1H, NH, exchanges with deuterium oxide). ^{13}C: 22.67 (C-6 Me), 29.85 (C-3), 49.33 (C-6), 119.68 (C-4)^a, 122.20 (C-5)^a, 126.15 (phenyl C-3, C-5),

					126.57 (phenyl C-4), 129.57 (phenyl C-2, C-6), 150.83 (phenyl C-1), 165.36 (C=N).
134b	H	*n*-Bu	Ph	3230 (NH), 1630 (C=C), 1589 (C=N).	^{1}H: 0.9 (t, J = 7Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.3 (m, 4H, $CH_2\mathit{CH_2}\mathit{CH_2}CH_3$), 1.55 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 3.08 (m, 2H, H-3), 4.01 (m, 1H, H-6), 5.78 (m, 2H, H-4, H-5), 7.3 (m, 5H, phenyl hydrogens), 8.6 (br s, 1H, NH, exchanges with deuterium oxide). ^{13}C: 13.8 ($CH_2CH_2CH_2\mathit{CH_3}$), 22.34 ($CH_2CH_2\mathit{CH_2}CH_3$), 26.38 ($CH_2\mathit{CH_2}CH_2CH_3$), 30.54 ($\mathit{CH_2}CH_2CH_2CH_3$), 36.05 (C-3), 53.13 (C-6), 120.61 (C-4)^a, 124.98 (C-5)^a, 126.14 (phenyl C-3, C-5), 128.64 (phenyl C-4), 131.93 (phenyl C-2, C-6), 142.71 (phenyl C-1), 163.56 (C-2).

134c	H	Ph	Ph	3221 (NH), 1614 (C=C), 1580 (C=N).	^{1}H: 3.28 (m, 2H, H-3), 5.14 (m, 1H, H-6), 5.89 (m, 2H, H-4, H-5), 7.2-7.6 (m, 10H, phenyl hydrogens), 8.6 (br s, 1H, NH, exchanges with deuterium oxide).
134d	Me	H	Ph	1600 (C=C), 1580 (C=N).	^{1}H: 3.2 (s, 3H, NMe), 3.76 (m, 2H, H-3), 4.08 (m, 2H, H-6), 5.88 (m, 2H, H-4, H-5), 7.3-7.5 (m, 5H, phenyl hydrogens).
134e	Me	Me	Ph	1600 (C=C), 1570 (C=N).	^{1}H: 1.3 (d, J = 7Hz, 3H, C-6 Me), 3.08 (s, 3H, NMe), 3.45 (d, J = 21Hz of d, J = 4Hz, 1H, H-3 ax), 3.85 (d, J = 2Hz of d, J = 2Hz of d, J = 21Hz, 1H, H-3eq), 4.0 (m, 1H, H-6), 5.75 (m, 2H, H-4, H-5), 7.26-7.4 (m, 5H, phenyl hydrogens).

134f	Me	*n*-Bu	Ph	1595 (C=C), 1580 (C=N).	^{1}H: 0.9 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}CH_3$), 1.04-1.38 (m, 4H, $\mathrm{CH_2}CH_2CH_2\mathrm{CH_3}$), 1.7 (M, 2H, $CH_2\mathrm{CH_2CH_2CH_3}$), 3.1 (s, 3H, NMe), 3.44 (d, J = 2.8Hz of d, J = 2.8Hz of d, J = 25Hz, 1H, H-3ax), 3.9 (d, J = 3.7Hz of d, J = 3.7Hz of d, J = 25Hz, 1H, H-3 eq), 4.04 (m, 1H, H-6), 5.8 (m, 2H, H-4, H-5), 7.15-7.4 (m, 5H, phenyl hydrogens).
134g	Me	Ph	Ph	1645 (C=C), 1590 (C=N).	^{1}H: 2.96 (s, 3H, NMe), 3.75 (d, J = 4.4Hz of d, J = 21.2Hz, 1H, H-3ax), 3.96 (d, J = 3.3Hz of d, J = 3.3Hz of d, J = 21.2Hz, 1H, H-3 eq), 4.95 (m, 1H, H-6), 5.8 (m, 2H, H-4 H-5), 7.2-7.45 (m, 1OH, phenyl hydrogens).
134h	Me	H	Cl -4-C_6H_4	1598 (C=C, C=N).	^{1}H: 3.15 (s, 3H, NMe), 3.7 (m, 2H, H-3), 4.0 (m, 2H,

H-6), 5.8 (m, 2H, H-4, H-5), 7.3 (m, 4H, phenyl hydrogens).

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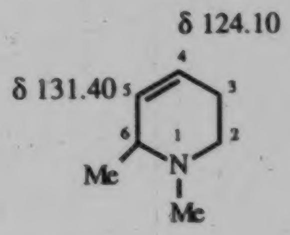
[a] Shift values were assigned with reference to 1,6-dimethyl-1,2,3,6-tetrahydropyridine (**142**).[333]


δ 124.10
δ 131.40
4
5
3
6
1
2
N
Me
Me

142

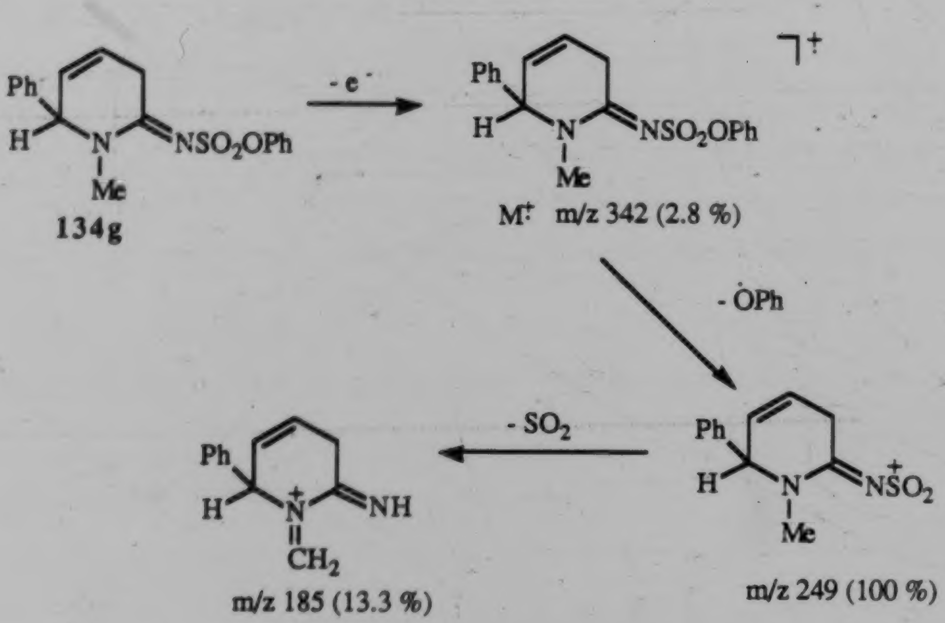
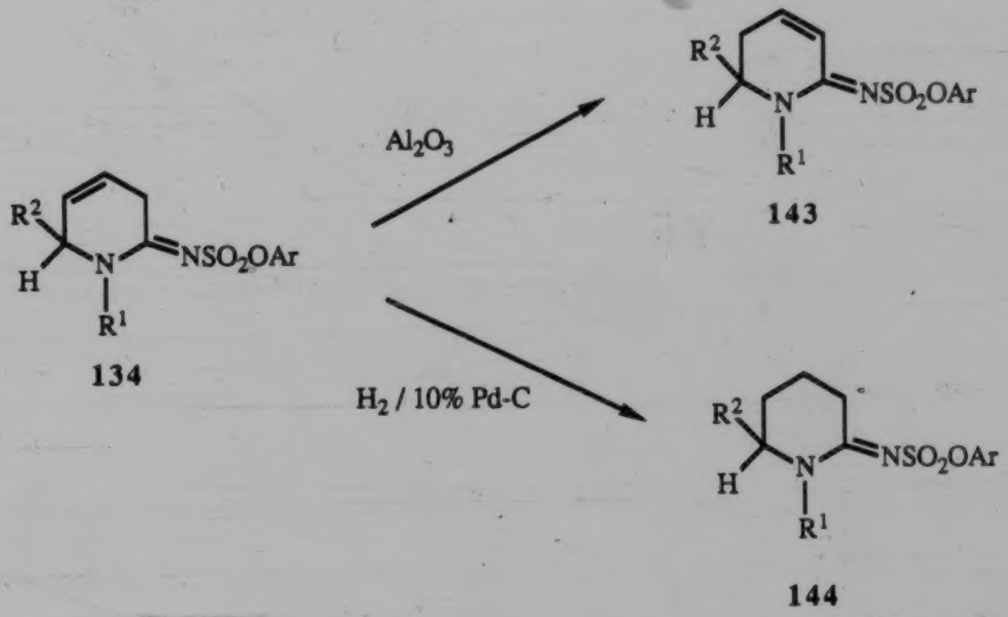

Ph
H
N
Me
NSO₂OPh
134g
- e⁻
M⁺˙ m/z 342 (2.8 %)
- ȮPh
m/z 249 (100 %)
- SO₂
CH₂
NH
m/z 185 (13.3 %)

Fig. 5: Some mass spactral fragments for compound **134g**.

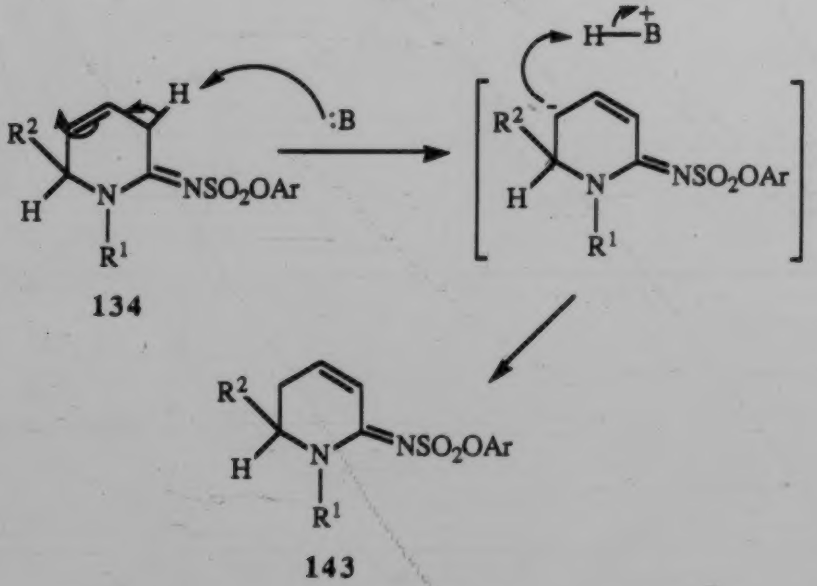
3.2.3.1.0.0. Isomerization of 1,2,3,6-tetrahydropyridylidene-2-aryloxysulfonamides (134a-g) to 1,2,5,6-tetrahydropyridylidene-2-aryloxysulfonamides (143a-g)

Treatment of the tetrahydropyridylidenes **134a-g** with a suspension of neutral aluminum oxide (Brockman Activity 1) in chloroform at 25 °C with stirring resulted in isomerization involving migration of the C_4-C_5 olefinic bond to the C_3-C_4 position. This isomerization reaction afforded the corresponding 1,2,5,6-tetrahydropyridylidene-2-phenoxysulfonamides (**143a-g**) in 62-98% chemical yields (Scheme 11, Table 6).



Scheme 11: Synthesis of 1,2,5,6-tetrahydropyridylidene-2-aryloxysulfonamides (**143a-g**) and piperidylidene-2-aryloxysulfonamides (**144a-h**).

A possible mechanism for this isomerization reaction could be as depicted below. One of the active C-3 hydrogens of **134** is abstracted to initiate the isomerization reaction. The C-3 hydrogens are active because they are allylic to the C_4-C_5 olefinic bond and adjacent (α) to the C=N moiety. However since alumina is generaaly regarded as a Lewis acid and the fact that the reaction also occurred in the presence of silica gel, suggest that this may not be the mechanism. The driving force for this isomerization reaction is likely due to the formation of **143** in which the C_3-C_4 olefinic bond is conjugated to the $C=N-SO_2$- moiety. Compounds **143** would be expected to have a lower ground state energy than compounds **134**.



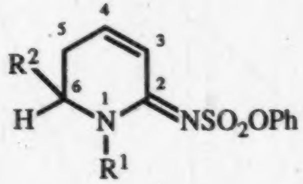
Compounds **134a-c** possessing a R^1 = H substituent (NH) required shorter reaction times for the isomerization reaction (24-48 hr), relative to compounds **134d-g** possessing a R^1 = Me substituent (NMe, 120 hr). One possible explanation for this difference in isomerization rates may be that the steric effect introduced by the NMe substituent alters the conformation of the molecule which hinders C-3 proton abstraction.

The IR absorption frequency for the C=N bond of compounds **143a-g** (Table 4) is lower than the C=N bond absorption frequency of the corresponding compounds **134a-g**

(Table 3) by approximately 10-50 cm^{-1}. This shift of IR absorption frequency reflects conjugation between the C_3-C_4 olefinic bond and the C=N moiety in compounds **143a-g**

The ^{1}H NMR spectral data (Table 4) for compounds **143a-g**, which are consistent with the assigned structures, indicate that replacing the NH proton of compounds **143a-c** by a *N*-methyl substituent (R^1 = Me) as in **143d-g**,induced a deshielding effect on the H-3 proton by about 1.0 δ (from δ 6.05-6.18 to δ 7.04-7.08). This could be due to the fact that the steric effect introduced by the methyl substituent (1,3-interaction) forces the molecule to adopt a conformation that orientates the H-3 proton such that it is deshielded by the ring

Table 4: IR and ^{1}H NMR Spectral Data for 1,2,5,6-Tetrahydropyridylidene-2-phenoxysulfonamides (142a-g).



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Entry	R^1	R^2	IR (KBr), cm^{-1}	^{1}H NMR ($CDCl_3$), δ
143a	H	Me	3250 (NH), 1645 (C=C), 1580 (C=N).	1.2 (d, J = 7Hz, 3H, C-6 Me), 2.12 (d, J = 3Hz of d, J = 6Hz of d, J = 12Hz of d, J = 18Hz, 1H, H-5ax), 2.45 (d, J = 4Hz of d, J = 5Hz of d, J = 18Hz, 1H, H-5eq), 3.65 (m, 1H, H-6), 6.1 (d, J = 3Hz of d, J = 10Hz, 1H, H-3), 6.7 (d, J = 4Hz of d, J = 6Hz of d, J = 10Hz, 1H, H-4), 7.35 (m, 5H, phenyl hydrogens), 7.65 (br s, 1H, NH, exchanges with deuterium oxide).
143b	H	*n*-Bu	3340 (NH), 1641 (C=C), 1570 (C=N).	0.9 (t, J = 6.5Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.3 (m, 4H, $\mathit{CH_2CH_2}CH_3$), 1.5 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 2.16 (d, J = 4.2Hz

				of d, J = 6Hz of d, J = 18.4Hz of d, J = 27.7Hz, 1H, H-5ax), 2.45 (d, J = 6Hz of d, J = 5Hz of d, J = 27.7Hz, 1H, H-5eq), 3.5 (m, 1H, H-6), 6.05 (br d, J = 10Hz, 1H, H-3), 6.7 (d, J = 4.2Hz of d, J = 6Hz of d, J = 10Hz, 1H, H-4), 7.36 (m, 5H, phenyl hydrogens), 7.8 (br s, 1H, NH, exchanges with deuterium oxide).
143c	H	Ph	3310 (NH), 1640 (C=N) 1570 (C=N).	2.5 (d, J = 2Hz of d, J = 4Hz of d, J = 12Hz of d, J = 18Hz, 1H, H-5ax), 2.68 (d, J = 6Hz of d, J = 6Hz of d, J = 18Hz, 1H, H-5 eq), 4.65 (d, J = 6Hz of d, J = 12Hz, 1H, H-6), 6.18 (br d, J = 10Hz, 1H, H-3), 6.75 (d, J = 4Hz of d, J = 6Hz of d, J = 10Hz, 1H, H-4). 7.25-7.46 (m, 10H, phenyl hydrogens), 7.96 (br s, 1H, NH, exchanges with deuterium oxide).
143d	Me	H	1640 (C=C), 1560 (C=N)	2.48 (m, 2H, H-5), 3.16 (s,3H, NMe), 3.54 (t, J = 7.2Hz, 2H, H-6), 6.7 (d, J = 4Hz of d, J = 4Hz of d, J = 10Hz, 1H, H-4), 7.05 (br d, J = 10Hz, 1H, H-3), 7.24-7.4 (m, 5H, phenyl hydrogens).

143e	Me	Me	1640 (C=C), 1548 (C=N),	1.22 (d, J = 6.5Hz, 3H, C-6 Me), 2.4 (d, J = 2Hz of d, J = 7Hz of d, J = 18Hz, 1H, H-5 ax), 2.76 (d, J = 3Hz of d, J = 4Hz of d, J = 7.5Hz of d, J = 18Hz, 1H, H-5eq), 3.1 (s, 3H, NMe), 3.7 (m, 1H, H-6), 6.62 (m, 1H, H-4), 7.05 (d, J = 4Hz of d, J = 10Hz, 1H, H-3), 7.24-7.42 9 (m, 5H, phenyl hydrogens).
143f	Me	*n*-Bu	1645 (C=C),1550 (C=N).	0.9 (t, J = 7Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.3 (m, 4H, $CH_2\mathit{CH_2CH_2}CH_3$), 1.6 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 2.36 (d, J = 6Hz of d, J = 18Hz, 1H, H-5ax), 2.7 (d, J = 3Hz of d, J = 3Hz of d, J = 7.5Hz of d, J = 18Hz , 1H, H-5eq), 3.02 (s, 3H, NMe), 3.46 (m, 1H, H-6), 6.6 (d, J = 3Hz of d, J = 6Hz of d, J = 10Hz, 1H, H-4), 7.04 (d, J = 3Hz of d, J = 10Hz, 1H, H-3), 7.25-7.42 (m, 5H, phenyl hydrogens).
143g	Me	Ph	1640 (C=C), 1540 (C=N).	2.62 (d, J = 3Hz of d, J = 7Hz, of d, J = 18Hz, 1H, H-5ax), 3.08 (s, 3H, NMe), 3.15 (m, 1H, H-5eq), 4.7 (d, J = 3Hz of d, J =

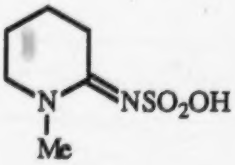
7Hz, 1H, H-6), 6.5 (m, 1H, H-4), 7.08 (d, J = 10Hz, 1H, H-3),
7.12-7.4 (m, 10H, phenyl hydrogens).

current effect of the phenyl ring. This possibility could be investigated by replacing the phenoxy group with an alkoxy substituent which is incapable of exhibiting a ring current anisotropic effect. The R^2 (Me, *n*-Bu or Ph) substituent of compounds **143a-c** (R^1 = H) appears to adopt an equatorial orientation, whereas the R^2 (Me, *n*-Bu or Ph) substituent of compounds **143e-g**, (R^1 = Me) appears to adopt an axial orientation. This is indicated by the fact that the width at half height[334] for the H-6 ^{1}H NMR signal of compounds **143a-c**, is greater than the width at half height for the H-6 signal of the corresponding compounds **143e-g** as shown by the following: **143a** (24Hz) > **143e** (18Hz); **143b** (30Hz) > **143f** (18Hz); **143c** (24Hz) > **143g** (15Hz). Moreover the H-6 proton for **143c** exhibited axial/axial (J = 12Hz) and axial/equatorial (J = 6Hz) couplings, whereas the H-6 proton of **143g** exhibited axial/equatorial (J = 7Hz) and equatorial/equatorial (J = 3Hz) couplings. This implies that the H-6 of **143c** is axial, whereas the H-6 of **143g** is equatorial.

The chemical yields and physical data for compounds **143a-g** are presented in Table 6.

3.2.3.2.0.0. Synthesis of piperidylidene-2-aryloxysulfonamides (144a-h)

Hydrogenation of compounds **134a-h** with hydrogen gas at 30 psi in the presence of 10 % palladium-on-charcoal using ethyl acetate as solvent at 25 °C afforded the corresponding piperidylidene-2-aryloxysulfonamides **144a-h** (Scheme 11) in 87-98%.chemical yields (Table 6). Methanol was found to be an unsuitable solvent for this hydrogenation since concomitant hydrogenolysis of the O-Ar bond resulted. Thus hydrogenation of compound **134d** using methanol as solvent afforded the sulfamic acid **145** in 83% chemical yield. Similar results have been reported for the hydrogenation of *p*-toluenesulfonyloxypyridines and quinolines,[335] and aryl *p*-toluenesulfonic acid esters [336] which yielded *p*-toluenesulfonic acid analogs. The effect of solvents upon catalytic hydrogenation has been reviewed.[337] The activity of a given catalyst in hydrogenation is generally increased by changing from a neutral, nonpolar solvent to a polar acidic solvent.[338]



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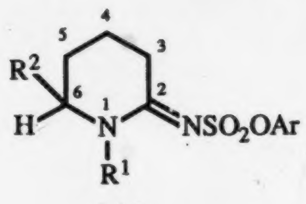
The IR and ^{1}H NMR spectral data for compounds **144a-h** summarized in Table 5 are consistent with their assigned structures. The absence of an olefinic bond in compounds **144a-h** is indicated by the absence of an absorption band in the 1620-1650 cm^{-1} region in their IR spectra. Furthermore, the ^{1}H NMR spectra do not display olefinic resonances in the δ 5-6 range.

Table 5: IR and ^{1}H NMR Spectral Data for Piperidylidene-2-aryloxysulfonamides (**144a-h**).



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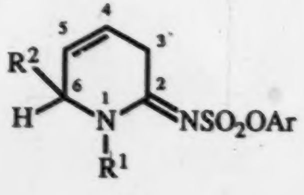
Entry	R^1	R^2	Ar	1R (KBr), cm^{-1}	^{1}H NMR ($CDCl_3$), δ
144a	H	Me	Ph	3240 (NH),1580 (C=N).	1.15 (d, J = 6Hz, 3H, C-6 Me), 1.55-1.95 (m, 4H, H-4, H-5), 2.35-2.65 (m, 2H, H-3), 3.45 (m, 1H, H-6), 7.36 (m, 5H, phenyl hydrogens), 8.1 (br s, 1H, NH, exchanges with deuterium oxide).
144b	H	*n*-Bu	Ph	3246 (NH), 1600 (C=N).	0.9 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}CH_3$), 1.2-2.0 (m, 10H, $CH_2CH_2CH_2\mathrm{CH_3}$, H-4, H-5), 2.35-2.66 (m, 2H, H-3), 3.3 (m, 1H, H-6), 7.35 (m, 5H, phenyl hydrogens), 8.24 (br s, 1H, NH, exchanges with deuterium oxide).

144c	H	Ph	Ph	3230 (NH), 1600 (C=N).	1.5-1.9 (m, 4H, H-4, H-5), 2.66 (m, 2H, H-3), 4.55 (m, 1H, H-6), 7.1 (m, 2H, *o*-phenyl hydrogens), 7.4 (m, 8H, phenyl hydrogens). 8.44 (br s, 1H, NH, exchanges with deuterium oxide).
144d	Me	H	Ph	1580 (C=N)	1.8 (m, 4H, H-4, H-5), 2.9-3.05 (m, 5H, H-3, NMe), 3.4 (m, 2H, H-6), 7.3 (m, 5H, phenyl hydrogens).
144e	Me	Me	Ph	1580 (C=N)	1.3 (d, J = 7Hz, 3H, C-6 Me), 1.6-1.2 (m, 4H, H-4, H-5), 3.0 (d, J = 7.2Hz of d, J = 19.2Hz, 1H, H-3ax), 3.05 (s, 3H, NMe), 3.2 (d, J = 4Hz of d, J = 4Hz of d, J = 19.2Hz, 1H, H-3eq), 3.6 (m, 1H, H-6), 7.28 (m, 2H, *o*-phenyl hydrogens), 7.4 (m, 3H, *m*- and *p*-phenyl hydrogens),
144f	Me	*n*-Bu	Ph	1560 (C=N)	0.9 (t, J = 7Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.2-1.55

					(m, 6H, $CH_2CH_2CH_2CH_3$), 1.65-1.85 (m, 4H, H-4, H-5), 2.9-3.2 (m, 5H, H-3, NMe), 3.35 (m, 1H, H-6), 7.2-7.45 (m, 5H, phenyl hydrogens)
144g	Me	Ph	Ph	1550 (C=N)	1.72 (m, 2H, H-4), 1.9 (m, 1H, H-5), 2.21 (m, 1H, H-5), 2.95 (s, 3H, NMe), 3.1 (d, J = 8Hz of d, J = 8Hz of d, J = 18Hz, 1H, H-3ax), 3.3 (d, J = 6Hz of d, J = 6Hz of d, J = 18Hz, 1H, H-3eq), 4.66 (t, J = 6Hz, 1H, H-6), 7.12 (d, J = 9Hz, 2H, *o*-phenyl hydrogens), 7.32-7.48 (m, 8H, phenyl hydrogens).
144h	Me	H	Cl-4-C_6H_4	1570 (C=N)	1.7-1.9(m, H-4, H-5), 2.9-3.15 (m, 2H, H-3), 3.05 (s, 3H, NMe), 3.45 (m, 2H, H-6), 7.36 (m, 4H, phenyl hydrogens).

Table 6: Physical and Pharmacological Data for Aryloxysulfonamides (134, 143 and 144).



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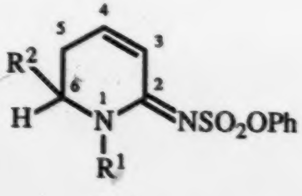
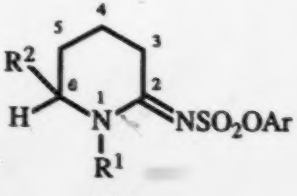


143



144

Entry	R^1	R^2	Ar	MP, ^{o}C	% Yield	Formula	Microanalysis: Calcd.(Found) C	H	N	Analgesic Activity^a,% Inhib.
134a	H	Me	Ph	102-103	78	$C_{12}H_{14}N_2O_3S$	54.12(54.16)	5.29(5.15)	10.52(10.42)	47.5 ±6.5
134b	H	*n*-Bu	Ph	85-86	98	$C_{15}H_{20}N_2O_3S$	58.42(58.23)	6.53(6.51)	9.08(9.00)	37.1±9.1
134c	H	Ph	Ph	136-137	95	$C_{17}H_{16}N_2O_3S$	62.18(61.88)	4.91(4.92)	8.53(8.29)	37.5±3.6
134d	Me	H	Ph	80-81	75	$C_{12}H_{14}N_2O_3S$	54.12(53.72)	5.29(5.23)	01.52(10.56)	27.7±5.3
134e	Me	Me	Ph	69-70	80	$C_{13}H_{16}N_2O_3S$	55.70(55.72)	5.75(5.61)	9.99(9.95)	24.2±4.2
134f	Me	*n*-Bu	Ph	59-60	61	$C_{16}H_{22}N_2O_3S$	59.60(59.20)	6.74(6.72)	8.68(8.47)	40.2±4.9
134g	Me	Ph	Ph	120-121	80	$C_{18}H_{18}N_2O_3S$	63.14(63.08)	5.30(5.34)	8.18(8.19)	30.5±7.5
134h	Me	Ph	Cl-4-C_6H_4	85^b	65	$C_{12}H_{13}N_2O_3SCl$	47.92(47.88)	4.32(4.33)	9.31(9.28)	NT^c
143a	H	Me	Ph	75-76	98	$C_{12}H_{14}N_2O_3S$	54.12(54.52)	5.29(5.55)	10.52(10.41)	53.7±8.1

143b	H	*n*-Bu	Ph	70-71	65	$C_{15}H_{20}N_2O_3S$	58.42(58.12)	6.53(6.53)	9.08(8.80)	52.5±16.0
143c	H	Ph	Ph	135-136	86	$C_{17}H_{16}N_2O_3S$	62.18(62.05)	4.91(5.06)	8.53(8.48)	41.1±5.2
143d	Me	H	Ph	76-77	80	$C_{12}H_{14}N_2O_3S$	54.12(53.88)	5.29(5.31)	10.52(10.16)	37.5±6.2
143e	Me	Me	Ph	56-57	90	$C_{13}H_{16}N_2O_3S$	55.70(55.61)	5.75(5.65)	9.99(9.84)	63.8±11.9
143f	Me	*n*-Bu	Ph	55-56	60	$C_{16}H_{22}N_2O_3S$	59.60(59.51)	6.74(6.74)	8.68(8.57)	48.3±7.6
143g	Me	Ph	Ph	125-126	61	$C_{18}H_{18}N_2O_3S$	63.14(63.05)	5.30(5.36)	8.18(8.00)	60.0±11.5
144a	H	Me	Ph	74-75	91	$C_{12}H_{16}N_2O_3S$	53.75(53.59)	6.01(6.01)	10.44(10.21)	57.7±5.4
144b	H	*n*-Bu	Ph	65-67	98	$C_{15}H_{22}N_2O_3S$	58.04(57.67)	7.14(6.95)	9.02(8.81)	67.5±13.5
144c	H	Ph	Ph	115-116	90	$C_{17}H_{18}N_2O_3S$	61.79(61.44)	5.49(5.42)	8.48(8.36)	47.2±5.6
144d	Me	H	Ph	59-60	95	$C_{12}H_{16}N_2O_3S$	53.75(53.42)	6.01(6.07)	10.44(10.23)	46.1±4.2
144e	Me	Me	Ph	70-71	90	$C_{13}H_{18}N_2O_3S$	55.30(55.46)	6.42(6.33)	9.92(9.81)	65.8±10.5
144f	Me	*n*-Bu	Ph	oil	89	$C_{16}H_{24}N_2O_3S$	59.23(59.46)	7.45(7.42)	8.63(8.55)	67.6±9.2
144g	Me	Ph	Ph	125-127	87	$C_{18}H_{20}N_2O_3S$	62.77(62.70)	5.85(5.86)	8.13(8.13)	79.6±8.3
144h	Me	Ph	Cl-4-C_6H_4	76-77	98	$C_{12}H_{15}N_2O_3S$	47.60(47.60)	4.99(5.00)	9.25(9.25)	53.3.1±9.1
Aspirin										58.0±7.2
Meperidine										0.6±0.08[d]

---

[a] Inhibition of 4% NaCl induced writhing in rats. The result is the mean ±SEM (standard error of the mean)for five animals at a dose of

50 mg/kg sc.

[b] Melting pont (decompostion).

[c] NT = Not tested.

[d] ED_{50} value.

Some major mass spectral fragments for compounds **144e** and their possible origin are illustrated in Fig. 6. An important fragmentation pathway of the molecular ion is the loss of the phenoxy substituent attached to the sulfonyl moiety.

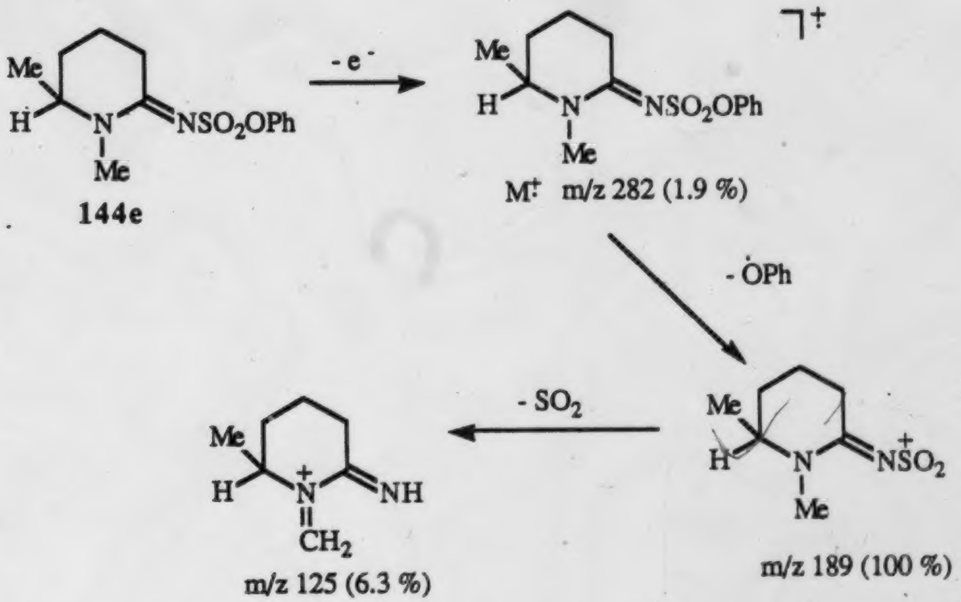
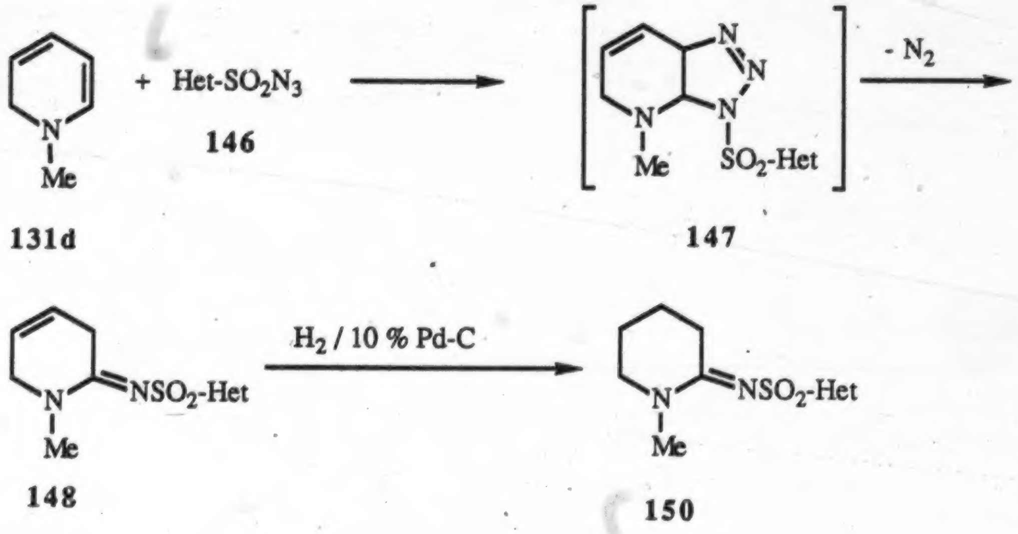

Me
H
N
NSO₂OPh
Me
144e
- e⁻
Me
H
N
NSO₂OPh
Me
M⁺ m/z 282 (1.9 %)
- ȮPh
Me
H
N
NSO₂
Me
m/z 189 (100 %)
- SO₂
Me
H
N
NH
CH₂
m/z 125 (6.3 %)

Fig. 6: Some mass spectral fragments for compound **144e**

3.2.4.0.0.0. Synthesis of 1-Methyl-1,2,3,6-tetrahydropyridylidene-2-(pyridyl)sulfonamides (148a-c).

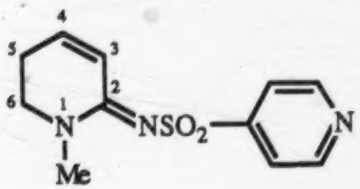
The regiospecific 1,3-dipolar cycloaddition reaction [251-253] of 1-methyl-1,2-dihydropyridine **(131d)** with pyridinesulfonyl azides **146a-c** afforded 1-methyl-1,2,3,6-tetrahydropyridylidene-2-(pyridyl)sulfonamides **(148a-c)** in 80-98% chemical yields (Scheme 12, Table 8).



a, Het = 2-pyridyl
b, Het = 3-pyridyl
c, Het = 4-pyridyl

Scheme 12: Synthesis of tetrahydropyridylidene- (**148a-c**) and piperidylidene-2-(pyridyl)sulfonamides (**150a-c**).

The IR and ^{1}H NMR spectra for compounds **148a-c** (Table 7) are similar to those of compounds **134d** except for differences in the chemical shifts of the pyridine ring protons of **148a-c** and the phenyl ring of **134d** (Table 3). The ^{13}C NMR spectrum of compound **148b** (Table 7) indicated the presence of the C=N moiety which displayed a signal at δ 162.66. Compound **148c** readily isomerized to 1,2,5,6,-tetrahydropyridylidene-2-(4-pyridyl)sulfonamide (**149**) upon passing through a column of silica gel with ethyl acetate as eluent (compare isomerization of compounds **134a-g** to **143a-g**, section **3.2.3.1.0.0.**). The 1R, ^{1}H and ^{13}C NMR spectral data for compound **149** are summarized in Table 7, whereas its physical data are given in Table 8.



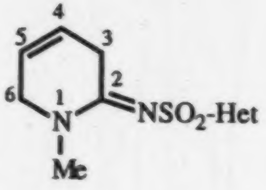
149

The new 2- (**146a**) and 4-pyridinesulfonyl (**146c**) azides were prepared from the corresponding sulfonyl chlorides by reaction with sodium azide in 95% ethanol (**146a**) or dry acetonitrile (**146c**). The 2- and 4-pyridinesulfonyl chlorides were prepared from the corresponding mercaptopyridines by chlorination using chlorine gas in the presence of concentrated hydrochloric acid below -5 °C, a method originally developed by Talik and Plazek[339] and used recently by Hanessian and Kagotani.[340] It has been reported that 2- and 4-pyridinesulfonyl chlorides, decompose readily by the loss of sulfur dioxide (SO_2) gas to give the corresponding chloropyridines.[341] Attempts to prepare 2- and 4-pyridinesulfonyl chlorides by reaction of the corresponding pyridinesulfonic acid with reagents such as phosphorous pentachloride (PCl_5) in the similar manner as the preparation of 3-pyridinesulfonyl chloride from 3-pyridinesulfonic acid,[291] have been unsuccessful.[342,343]

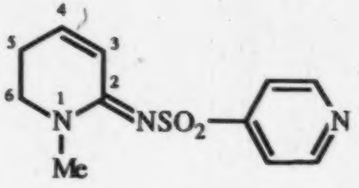
3.2.4.1.0.0. Synthesis of 1-Methylpiperidylidene-2-(pyridyl)sulfonamides (150a-c)

Compounds **150a-c** were prepared in 94-99 % yield by catalytic hydrogenation of the corresponding tetrahydropyridylidene (**148a-c**), using hydrogen gas a 35 psi and 10 % palladium-on-charcoal, in methanol at 25 °C (Scheme 12, Table 8). The IR and NMR spectral data for compounds **150a-c** (Table 7) are consistent with the assigned structures.

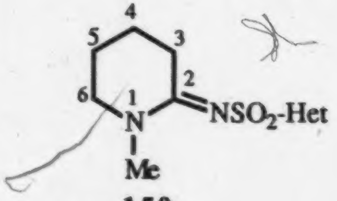
Table 7: IR and NMR Spectral Data for Tetrahydropyridylidene- and Piperidylidene-2-(pyridyl)sulfonamides (**148a-c**, **149** and **150a-c**).


1
2
3
4
5
6
N
Me
NSO$_2$-Het

148


1
2
3
4
5
6
N
Me
NSO$_2$
N

149


1
2
3
4
5
6
N
Me
NSO$_2$-Het

150

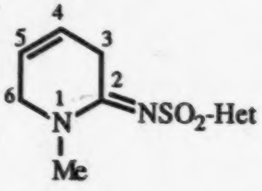
Entry	Het	IR (KBr), cm^{-1}	NMR (CDCl$_3$), δ
148a	2-pyridyl	1642 (C=C), 1581 (C=N).	^{1}H: 3.14 (s, 3H, NMe), 3.92 (m, 2H, H-3), 4.0 (m, 2H, H-6), 5.74-5.84 (m, 2H, H-4, H-5), 7.45 (d, J = 2Hz of d, J = 5.5Hz of d, J = 8Hz,1H, pyridine H-5), 7.9 (d, J = 2Hz of d, J = 8 of d, J = 8Hz, 1H, pyridine H-4), 8.13 (d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-3), 8.72 (d, J = 5.5Hz, 1H, pyridine H-6).
148b	3-pyridyl	1641(C=C), 1581 (C=N).	^{1}H: 3.1 (s, 3H, NMe), 3.72 (m, 2H, H-3), 4.0 (m, 2H, H-6), 5.74-5.8 (m, 2H, H-4, H-5), 7.44 (d, J = 8Hz of d, J = 6Hz, 1H, pyridine H-5),

			8.26 (d, J = 2Hz of d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.76 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6), 9.24 (d, J = 2Hz, 1H, pyridine H-2). ^{13}C: 28.69 (C-6), 37.49 (NMe), 50.43 (C-3), 119.44 (C-4 or C-5), 120.25 (C-4 or C-5), 122.97 (pyridine C-5), 133.49 (pyridine C-4), 140.06 (pyridine C-3), 147.06 (pyridine C-6), 151.67 (pyridine C-2), 162.66 (C-2).
148c	4-pyridyl	1641(C=C), 1581 (C=N).	^{1}H: 3.06 (s, 3H, NMe), 3.66 (m, 2H, H-3), 3.88 (m, 2H, H-6), 5.74 (m, 2H, H-4, H-5), 7.8 (d, J = 2Hz of d, J = 6Hz 2H, pyridine H-3, H-5), 8.76 (d, J = 2Hz of d, J = 6 Hz, m, 2H, pyridine H-2, H-6).
149	4-pyridyl	1638 (C=C), 1581 (C=N).	^{1}H: 2.42 (m, 2H, H-5), 3.07 (s, 3H, NMe), 3.46 (t, J = 7.4Hz, 2H, H-6), 6.68 (d, J = 4.9Hz of d, J = 4.9Hz of d, J = 10.4Hz , 1H, H-4), 7.06 (d, J = 2Hz of d, J = 2Hz of d, J = 10.4Hz , 1H, H-3), 7.8 (d, J = 2Hz of d, J = 5Hz, 2H, pyridine H-3, H-5), 8.78 (d, J = 2Hz of d, J = 5Hz, 2H, pyridine H-2, H-6).

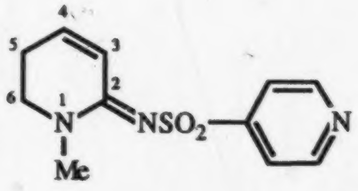
			^{13}C: 23.30 (C-5), 37.91 (NMe), 47.70.43 (C-6), 119.77 (C-3 or C-4), 120.40 (C-3 or C-4), 140.68 (pyridine C-3, C-5), 150.53 (pyridine C-2, C-6), 151.67 (pyridine C-4), 158.74 (C=N).
150a	2-pyridyl	1589 (C=N)	^{1}H: 1.75-1.85 (m, 4H, H-4, H-5), 3.06 (s, 3H, NMe), 3.24 (t, J = 7Hz, 2H, H-3), 3.38 (t, J = 6Hz, 2H, H-6), 7.43 (d, J = 8.5Hz of d, J = 6Hz, 1H, pyridine H-5), 7.86 (d, J = 8.5Hz of d, J = 8.5Hz, 1H, pyridine H-4), 8.09 (d, J = 8.5Hz, 1H, pyridine H-3), 8.86 (d, J = 8.5Hz, 1H, pyridine H-3), 8.86 (d, J = 6Hz, 1H, pyridine H-6).
150b	3-pyridyl	1589 (C=N)	^{1}H: 1.78-1.82 (m, 4H, H-4, H-5), 3.06 (s, 3H, NMe), 3.12 (t, J = 6Hz, 2H, H-3), 3.42 (t, J = 6Hz, 2H, H-6), 7.44 (d, J = 8Hz of d, J = 6Hz, 1H, pyridine H-5), 8.24 (d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.73 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6), 9.2 (s, 1H, pyridine H-2).
150c	4-pyridyl	1573 (C=N)	^{1}H: 1.76-1.88 (m, 4H, H-4, H-5), 3.06 (s, 3H, NMe), 3.1 (t, J = 6Hz,

2H, H-3), 3.42 (t, J = 6Hz, 2H, H-6), 7.82 (d, J = 6Hz, 2H, pyridine, H-3, H-5), 8.78 (d, J = 6Hz, 2H, pyridine H-2, H-6).

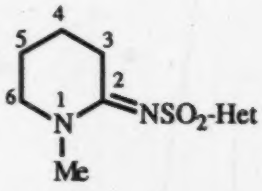
Table 8: Physical and Pharmacological Data for Tetrahydropyridylidene- and Piperidylidene-2-(pyridyl)sulfonamides (**148a-c**, **149** and **150a-c**).



148



149



150

Entry	Het	% Yield	MP, °C	Formula	Microanalysis: Calcd.(found)			Analgesic activity[a]
					C	H	N	ED_{50}, mg/kg sc.
148a	2-pyridyl	95	96-98	$C_{11}H_{15}N_3O_2S$	52.57(52.33)	5.21(5.36)	16.72(16.87)	NT[b]
148b	3-pyridyl	98	89-91	$C_{11}H_{15}N_3O_2S$	52.57(52.52)	5.21(5.33)	16.72(16.72)	NT
148c	4-pyridyl	80	83-85	$C_{11}H_{15}N_3O_2S$	52.57(52.44)	5.21(4.92)	16.72(16.40)	NT
149	4-pyridyl	90	75-77	$C_{11}H_{15}N_3O_2S$	52.57(52.30)	5.21(5.10)	16.72(16.42)	NT
150a	2-pyridyl	94	114-116	$C_{11}H_{17}N_3O_2S$	52.18(52.25)	5.97(6.07)	16.60(16.63)	6.2 (3.04-12.66)
150b	3-pyridyl	99	95-97	$C_{11}H_{17}N_3O_2S$	52.18(52.42)	5.97(6.18)	16.60(16.50)	9.0 (4.16-19.48)
150c	4-pyridyl	95	66-68	$C_{11}H_{17}N_3O_2S$	52.18(51.75)	5.97(5.95)	16.60(16.24)	6.6 (3.46-12.61)

Meperidine	0.6 (0.33-1.08)

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[a] % Inhibition of 4% NaCl-induced writhing in rats. The values in brackets are the 95% confidence limits.

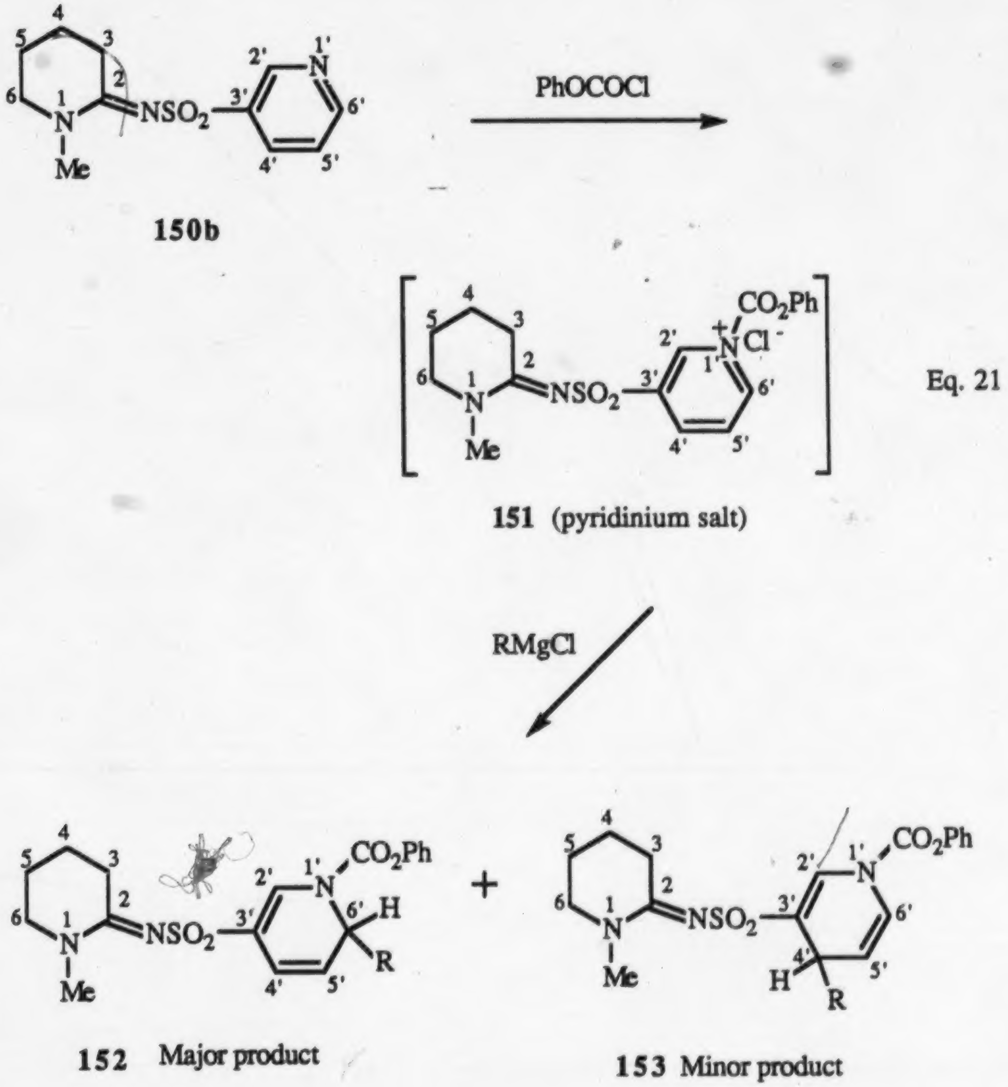
[b] NT = not tested.

3.2.4.1.1.0. Synthesis of 1-methylpiperidylidene-2-(1-phenoxycarbonyl-1,6(1,2)-dihydropyridyl)sulfonamides (152 and 154)

Recent investigations describing the synthesis of 1,2(1,6)-dihydropyridines by nucleophilic addition of Grignard reagents to 1-acylpyridinium salts have been reported.[212,213] Compounds **152a-d** were synthesized in 43-87% yields, by reaction of methyl, *n*-butyl, *t*-butyl or phenylmagnesium chloride with the 1-phenoxycarbonylpyridinium chloride salt (**151**) of compound **150b**, produced *in situ*, by the reaction of **150b** with phenyl chloroformate in dry tetrahydrofuran (THF) at -78 °C (Eq. 21). Compounds **152a-d** were stable crystalline solids possibly as a result of the electron-withdrawing sulfonyl moiety at the C-3' position.[193] In reactions where R was methyl, *n*-butyl or *t*-butyl, the respective 1,4-dihydropyridine isomers **153a-c** were isolated (TLC) as minor products.

These reactions were carried out at a low temperature (-78 °C) to minimize formation of the 1,4-dihydropyridine product, which is the product of thermodynamic control that is favored at higher temperatures.[205] The solvent employed is also a determinant of the ratio of 1,2 (1,6)- to 1,4-products[344]. Ether favours 1,2 and/or 1,6-dihydropyridine product formation relative to the 1,4-isomer, whereas the more polar THF favours 1,4-products.[344, 345] However, ether could not be used as solvent in these reactions employing **150b** due to the low solubility of **150b** in ether.

The nature of the nucleophilic reagent also influences the ratio of 1,2(1,6) to 1,4-dihydropyridine products. "Hard" nucleophiles preferentially attack the pyridinium salt at the α- (C-2' and C-6') positions to yield 1,2 and/or 1,6-dihydropyridine products, whereas "soft" nucleophiles add predominantly at the γ- (C-4') position to afford 1,4-dihydropyridines as the major products[346] The reaction of **150b** with phenylmagnesium chloride afforded only the 1,6-product **152d**. This is attributed to the fact that the phenyl group is a harder nucleophile than an alkyl group and attacks the pyridinium salt preferentially at the α-position of the pyridine ring. Lyle and White[347] have reported that reaction of 1-alkylpyridinium salts with phenylmagnesium bromide afforded 2-phenyl-1-alkyl-1,2-dihydropyridines as the sole products.



150b

151 (pyridinium salt)

Eq. 21

152 Major product

153 Minor product

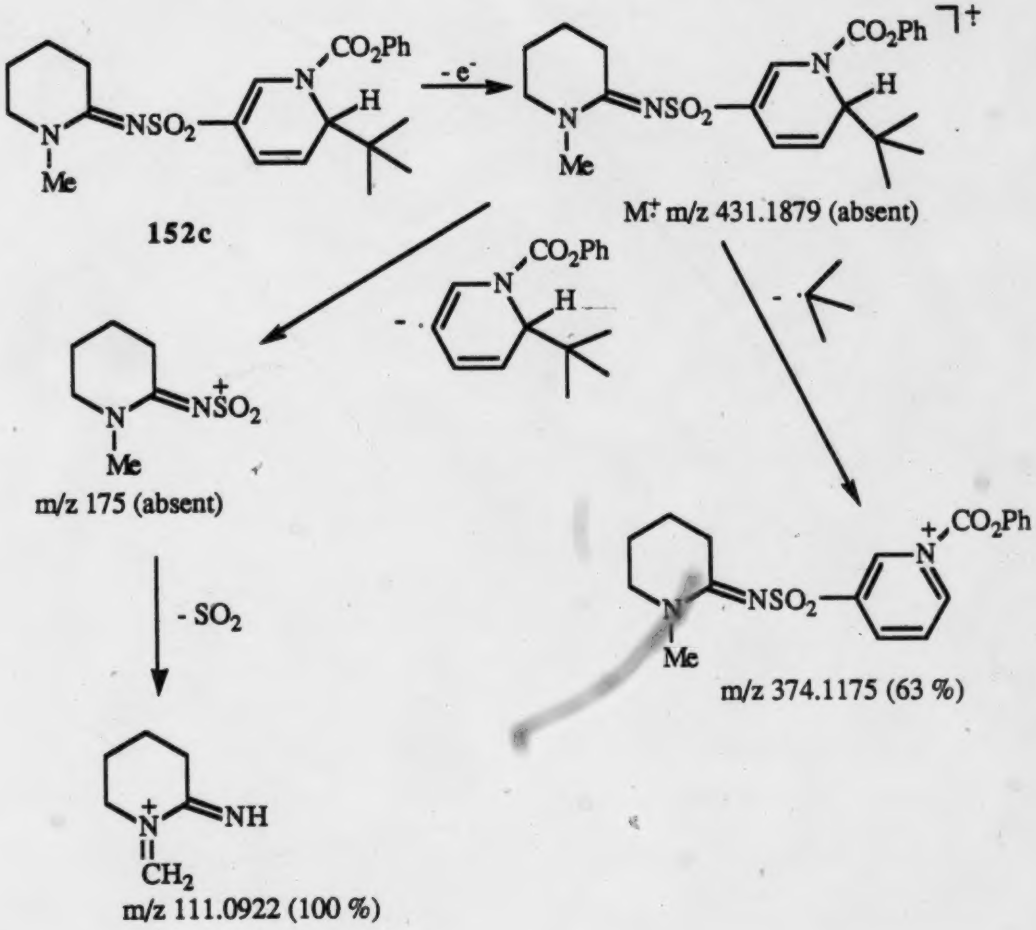
R = Me, *n*-Bu, *t*-Bu, Ph.

The ratio of 1,6-: 1,4- (**152** : **153**) products isolated (preparative silica gel TLC), using the alkylmagnesium chlorides were Me (3 : 1), *n*-Bu (3 : 2) and *t*-Bu (3.5 : 2). The reaction employing methylmagnesium chloride afforded the highest 1,6- to 1,4- product ratio. This is a reflection of the fact that CH_3^- is the "hardest" of the three nucleophiles CH_3^-, $CH_3(CH_2)_2CH_2$- and $C(CH_3)_3^-$. The slightly higher 1,6- : 1,4-product ratio obtained for the reaction employing *t*-butylmagnesium Chloride relative to *n*-butylmagnesium chloride which provides a "harder" nucleophilic species, is attributed to the greater steric effect of the *t*-Bu substituent, which must hinder attack at the C-4' position.

1,2-Dihydropyridine products were not obtained in these reactions. This is attributed to the greater steric hindrance at the C-2' relative to C-6' of the pyridinium salt (**151**), due to the closer proximity of the C-2' position to the sulfonyl moeity. Steric hindrance has been reported to be a major factor which prevented the formation of 1,2-dihydropyridine products in reactions of Grignard reagents with 1-acylpyridinium salts.[348]

The IR spectra (Table 9) for compounds **152a-d**, and **153a-c** displayed carbonyl (1728-1737 cm^{-1} range), olefinic (1638 cm^{-1}) and imino (1573-1581 cm^{-1} range) absorption bands. The 1H NMR spectra (Table 9) for compounds **152a-d**, and **153a-c** displayed chemical shifts for the piperidine ring protons similar to those for compounds **150a-c** (Table 7). The chemical shifts and coupling constants (J values) for the dihydropyridine ring protons of **152a-d** and **153a-c** are also consistent with the assigned 1,6- and 1,4-dihydropyridine ring systems respectively.[179,193]

Some major fragments present in the high resolution mass spectrum for compound **152c**, and their possible origin are shown in Fig. 7. The loss of a C-4' or C-6' alkyl, or phenyl substituent from the molecular ion appears to be a major fragmentation pathway in the electron impact mass spectra of these dihydropyridines (**152** and **153**). A similar observation in the electron impact mass spectra of 1,4-(dihydropyridine) analogs of nifedipine has been reported.[349]

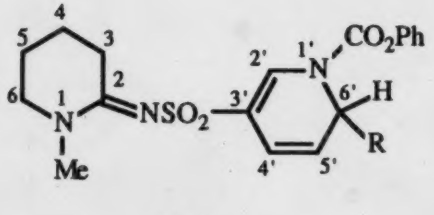

CO₂Ph
NSO₂
N
H
Me
- e⁻
]+
M⁺ m/z 431.1879 (absent)
- ·
- ·
m/z 175 (absent)
- SO₂
m/z 374.1175 (63 %)
NH
CH₂
m/z 111.0922 (100 %)

152c

Fig 7: Some mass spectral fragments for compound **152c**.

Treatment of compound **150c** with phenyl chloroformate and sodium borohydride ($NaBH_4$) in methanol at -78 ^{o}C afforded the dihydropyridine product **154a** in 44 % chemical yield (Eq. 22).

Table 9: IR and ^1H NMR Spectral Data for 1-Methylpiperidylidene-2-(dihydropyridine)sulfonamides (**152a-d** **153a-c** and **154a-e**).


1
2
3
4
5
6
N
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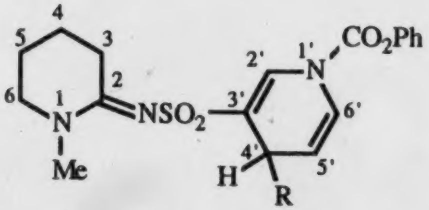
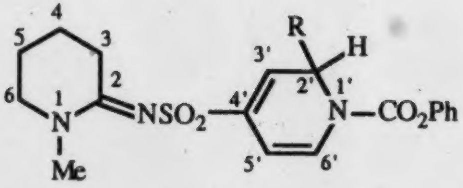
2'
3'
4'
5'
6'
N
CO$_2$Ph
H
R

152


1
2
3
4
5
6
N
Me
NSO$_2$
1'
2'
3'
4'
5'
6'
N
CO$_2$Ph
H
R

153


1
2
3
4
5
6
N
Me
NSO$_2$
1'
2'
3'
4'
5'
6'
N
CO$_2$Ph
R
H

154

Entry	R	IR, cm^{-1}	^1H NMR ($CDCl_3$), δ^a
152a	Me	1737 (C=O), 1638 (C=C), 1573 (C=N).	25 °C: 1.3 (d, J = 7Hz, 3H, C-6' Me), 1.8 (m, 4H, H-4, H-5), 3.1 (s, 3H, NMe), 3.15 (m, 2H, H-3), 3.4 (t, J = 6.5Hz, 2H, H-6), 4.98 (m, 1H, H-6'), 5.74 (d, J = 5.1Hz of d, J = 8.5Hz, 1H, H-5'), 6.35 (d, J = 8.5 Hz, 1H, H-4'), 7.15 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.24 (d, J = 8.5Hz, 1H, *p*-phenyl hydrogen), 7.4 (t, J = 8.5 Hz, 2H, *m*-phenyl hydrogens), 7.78 (s, 1H, H-2').

152b	*n*-Bu	1737 (C=O), 1638 (C=C), 1573 (C=N).	25 ^{o}C: 0.9 (t, J = 6Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.34 (m, 4H, $CH_2CH_2CH_2$ CH_3), 1.6 (m, 2H, CH_2 $CH_2CH_2CH_3$), 1.8 (m, 4H, H-4, H-5), 3.04 (s, 3H, NMe), 3.12 (m, 2H, H-3), 3.38 (t, J = 6.4Hz, 2H, H-6), 4.9 (m, 1H, H-6'), 5.79 (d, J = 6Hz of d, J = 8Hz, 1H, H-5'), 6.45 (d, J = 8Hz, 1H, H-4'), 7.14 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.25 (t, J = 8.5Hz, 1H, *p*-phenyl hydrogen), 7.4 (t, J = 8.5Hz, 2H, *m*-phenyl hydrogens), 7.8 (s, 1H, H-2').
152c	*t*-Bu	1728 (C=O), 1638 (C=C), 1573 (C=C).	25 ^{o}C: 0.98 (s, 9H $C(CH_3)_3$), 1.75-1.86 (m, 4H, H-4, H-5), 3.04 (s, 3H, NMe), 3.14 (t, J = 7Hz, 2H, H-3), 3.4 (t, J = 6Hz, 2H, H-6), 4.8 (d, J = 6Hz, 1H, H-6'), 5.8 (d, J = 6Hz of d, J = 8.5Hz, 1H, H-5'), 6.54 (d, J = 8.5Hz, 1H, H-4'), 7.16 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.26 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.42 (t, J = 8Hz, 2H, *m*-phenyl hydrogens), 7.9 (s, 1H, H-2')

152d	Ph	1737 (C=O), 1638 (C=C), 1573 (C=N).	25 ^{o}C: 1.8 (m, 4H, H-4, H-5), 3.04-3.16 (m, 5H, NMe, H-3), 3.38 (t, J = 6Hz, 2H, H-6), 5.84 (d, J = 5.5Hz of d, J = 8.5Hz, 1H, H-5'), 5.96 (d, J = 5.5Hz, 1H, H-6'), 6.54 (d, J = 8.5Hz, 1H, H-4'), 7.22-7.5 (m, 10H, OPh, Ph), 7.9 (s, 1H, H-2').
153a	Me	1737 (C=O), 1638 (C=C), 1581 (C=N).	25 ^{o}C: 1.44[1.52] (d, J = 7Hz, 3H, C-4' Me), 1.84 (m, 4H, H-4, H-5), 3.06[3.05] (s, 3H, NMe), 3.14 (m, 2H, H-3), 3.4 (t, J = 6.5Hz, 2H, H-6), 3.63 (m, 1H, H-4'), 5.7 [5.62] (m, 1H, H-5'), 7.06[7.0] (d, J = 6Hz, 1H, H-6'), 7.17 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.28 (d, J = 8.5Hz, 1H, *p*-phenyl hydrogen), 7.42 (t, J = 8.5 Hz, 2H, *m*-phenyl hydrogens), 8.0[7.96] (s, 1H, H-2'). Rotameric ratio = 11 : 5.with reference to H-2' dual peaks.
153b	*n*-Bu	1737 (C=O), 1638 (C=C), 1564 (C=N).	25 ^{o}C: 0.88 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}CH_3$), 1.24-1.42 (m,

4H, $\mathrm{CH_2}\mathit{CH_2CH_2}\,\mathrm{CH_3}$), 1.56 (m, 2H, $\mathit{CH_2}\,\mathrm{CH_2CH_2CH_3}$), 1.8 (m, 4H, H-4, H-5), 3.04(s, 3H, NMe), 3.11 (m, 2H, H-3), 3.36 (t, J = 6Hz, 2H, H-6), 3.64 (m, 1H, H-4'), 5.36 (br, 1H, H-5'), 7.03 (br, 1H, H-6'), 7.14 (d, J = 8.3Hz, 2H, *o*-phenyl hydrogens), 7.24 (t, J = 8.3Hz, 1H, *p*-phenyl hydrogen), 7.38 (t, J = 8.3Hz, 2H, *m*-phenyl hydrogens), 8.02[7.97] (s, 1H, H-2'). Rotameric ratio = 5 : 3 with reference to H-2' dual peaks.

61 ^{o}C: 0.88 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.24-1.5 (m, 6H, $\mathit{CH_2CH_2CH_2}\,\mathrm{CH_3}$), 1.75 (m, 4H, H-4, H-5), 3.0 (s, 3H, NMe), 3.06 (m, 2H, H-3), 3.36 (t, J = 6Hz, 2H, H-6), 3.64 (m, 1H, H-4'), 5.12 (d, J = 4.5Hz of d, J = 7.5Hz, 1H, H-5'), 6.91 (d, J = 7.5Hz, 1H, H-6'), 7.14 (d, J = 8.3Hz, 2H, *o*-phenyl hydrogens), 7.24 (m, 1H, *p*-phenyl hydrogen), 7.38 (t, J = 8.3Hz, 2H, *m*-phenyl hydrogens), 8.0 (s, 1H, H-2'). Complete coalescence occurred.

153c	*t*-Bu	1728 (C=O), 1704 (C=C), 1573 (C=N).	25 °C: 1.02 (s, 9H, $C(CH_3)_3$), 1.8 (m, 4H, H-4, H-5), 3.1 (s, 3H, NMe), 3.2 (m, 2H, H-3), 3.37 (t, J = 6Hz, 2H, H-6), 3.45 (d, J = 6Hz, 1H, H-4'), 5.34 (m, 1H, H-5'), 6.83 (d, J = 7.2Hz, 1H, H-6'), 7.15-7.26 (m, 3H, *o*- and *p*-phenyl hydrogens), 7.38 (t, J = 8.5Hz, 2H, *m*-phenyl hydrogens), 8.12 (br, 1H, H-2'). No separate rotameric peaks observed but H-2' peak was broad, indicating incomplete coalescence. 61 °C: 0.96 (s, 9H, $C(CH_3)_3$), 1.8 (m, 4H, H-4, H-5), 2.96-3.06 (m, 5H, NMe, H-3), 3.28 (t, J = 6Hz, 2H, H-6), 3.38 (d, J = 1.2Hz of d, J = 6Hz, 1H, H-4'), 5.24 (d, J = 6Hz of d, J = 7.2Hz, 1H, H-5'), 6.96 (d, J = 1.2Hz of d, J = 7.2Hz, 1H, H-6'), 7.06-7.18 (m, 3H, *o*- and *p*-phenyl hydrogens), 7.3 (m, 2H, *m*-phenyl hydrogens), 8.06 (s, 1H, H-2'). Complete coalescence occurred.

154a	H	1729 (C=O), 1638 (C=C), 1573 (C=N).	25 °C: 1.75 (m, 4H, H-4, H-5), 3.0[2.98] (s, 3H, NMe), 3.03 (t, J = 7Hz, 2H, H-3), 3.33 (t, J = 6Hz, 2H, H-6), 4.55[4.7] (d, J = 4.5Hz, 2H, H-2'), 5.57[5.6] (d, J = 1Hz of d, J = 8Hz, 1H, H-5'), 6.33 (m, 1H, H-3'), 6.96[6.89] (d, J = 8Hz, 1H, H-6'), 7.07 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.24 (t,J = 8.5Hz, 1H, *p*-phenyl hydrogen), 7.33 (t, J = 8.5Hz, 2H, *m*-phenyl hydrogens). Rotameric ratio = 5 : 3 with reference to H-2' dual peaks. 61°C: 1.85 (m, 4H, H-4, H-5), 2.99 (s, 3H, NMe), 3.13 (t, J = 7Hz, 2H, H-3), 3.38 (t, J = 6Hz, 2H, H-6), 4.66 (br, 2H, H-2'), 5.58 (d, J = 8Hz, 1H, H-5'), 6.36 (m, 1H,H-3'), 6.94 (d, J = 8Hz, 1H, H-6'), 7.16 (d,J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.24 (t, J = 8.5Hz, 1H, *p*-phenyl hydrogen),7.38 (t, J = 8.5Hz, *m*-phenyl hydrogens). Incomplete coalescence of H-2' peak.

154b	Me	1729 (C=O), 1638 (C=C), 1540 (C=N).	25 °C: 1.23[1.3] (d, J = 7.2Hz, 3H, C-2' Me), 1.75 (m, 4H, H-4, H-5), 3.0[2.98] (s, 3H, NMe), 3.04 (m, 2H, H-3), 3.32 (t, J = 6.5Hz, 2H, H-6), 5.06[5.12] (m, 1H, H-2'), 5.68[5.73] (d, J = 1.2Hz of d, J = 7.9Hz, 1H, H-5'), 6.34 (d, J = 1.2Hz of d, J = 6Hz, 1H, H-3'), 6.92[6.85] (d, J = 7.9Hz, 1H, H-6'), 7.08 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.18 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.33 (t, J = 8Hz, 2H, *m*-phenyl hydrogens).Rotameric ratio = 9 : 5 with reference to H-2' dual peaks. 61 °C: 1.26 (d, J = 7.2Hz, 3H, C-2' Me), 1.74 (m, 4H, H-4, H-5), 2.99 (s, 3H, NMe), 3.03 (t, J = 6Hz, 2H, H-3), 3.3 (t, J = 6.5Hz, 2H, H-6), 5.07 (m, 1H, H-2'), 5.69 (d, J = 7.9Hz, 1H, H-5'), 6.31 (d, J = 6Hz, 1H, H-3'), 6.87 (d, J = 7.9Hz, 1H, H-6'), 7.08 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.3 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.42 (t, J = 8Hz, 2H, *m*-phenyl hydrogens). Complete coalescence occurred.

154c	*n*-Bu	1729 C=O), 1638 (C=C), 1548 (C=N).	25 °C: 0.88[0.92] (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.28-1.44 (m, 5H, $\mathit{CH}\mathrm{H}\mathit{CH_2CH_2}\mathrm{CH_3}$), 1.66 (m, 1H, $\mathit{CH}\mathrm{HCH_2CH_2CH_3}$), 1.84 (m, 4H, H-4, H-5), 3.08[3.06] (s, 3H, NMe), 3.13 (t, J = 6Hz, 2H, H-3), 3.39 (t, J = 6.5Hz, 2H, H-6), 5.06[5.12] (q, J = 6Hz, 1H, H-2'), 5.78[5.83] (d, J = 1.5Hz of d, J = 8Hz, 1H, H-5'), 6.47 (d, J = 6Hz, 1H, H-3'), 7.02[6.9] (d, J = 8Hz, 1H, H-6'), 7.14 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogens), 7.26 (m, 1H, *p*-phenyl hydrogens), 7.4 (t, J = 8.5Hz, 2H, *m*-phenyl hydrogens). Rotameric ratio = 7 : 4 with reference to H-6' dual peaks. 61 °C: 0.91 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.3-1.45 (m, 5H, $\mathit{CH}\mathrm{H}\mathit{CH_2CH_2}\mathrm{CH_3}$), 1.68 (m, 1H, $\mathit{CH}\mathrm{HCH_2CH_2CH_3}$), 1.84 (m, 4H, H-4, H-5), 3.07 (s, 3H, NMe), 3.12 (t, J = 6Hz, 2H, H-3), 3.38 (t, J = 6.5Hz, 2H, H-6), 5.08 (q, J = 6Hz, 1H, H-2'), 5.8 (d, J = 8Hz, 1H, H-5'), 6.47 (d, J = 1.5Hz of d, J = 6Hz, 1H, H-3'), 7.0 (d, J = 8Hz, 1H, H-6'), 7.16 (d, J = 8.5Hz,

			2H, *o*-phenyl hydrogens), 7.23 (t, J = 8.5Hz, 1H, *p*-phenyl hydrogens), 7.38 (t, J = 8.5Hz, 2H, *m*-phenyl hydrogens). Complete coalescence occurred.
154d	*t*-Bu	1729 (C=O), 1638 (C=C), 1574 (C=N).	25 °C: 0.98[1.13] (s, 9H, $C(CH_3)_3$), 1.83 (m, 4H, H-4, H-5), 3.05[3.03] (s, 3H, NMe), 3.11 (t, J = 6.5Hz, 2H, H-3), 3.38 (t, J = 6Hz, 2H, H-6), 4.92[4.96] (d, J = 6Hz, 1H, H-2'), 5.83[5.89] (d, J = 1.4Hz of d, J = 8Hz, 1H, H-5'), 6.5 (d, J = 6Hz, 1H, H-3'), 7.1[7.08] (d, J = 8Hz, 1H, H-6'), 7.15 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.25 (t, J = 8Hz, 1H, *p*-phenyl hydrogens), 7.4 (t, J = 8Hz, 2H, *m*-phenyl hydrogens). Rotameric ratio = 10 : 7 with reference to H-2' dual peaks. 61 °C: 1.03 (s, 9Hz, $C(CH_3)_3$), 1.84 (m, 4H, H-4, H-5), 3.05 (s, 3H, NMe), 3.13 (m, 2H, H-3), 3.38 (t, J = 6Hz, 2H, H-6), 4.95 (d, J = 6Hz, 1H, H-2'), 5.86 (d, J = 8Hz, 1H, H-5'), 6.5 (d, J = 1Hz of d, J = 1.4Hz of d, J = 6Hz, 1H, H-3'), 7.08 (d, J

			= 8Hz, 1H, H-6'), 7.16 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.23 (t, J = 8Hz, 1H, *p*-phenyl hydrogens), 7.4 (t, J = 8Hz, 2H, *m*-phenyl hydrogens). Complete coalescence occurred.
154e	Ph	1729 (C=O), 1638 (C=C), 1573 (C=N).	25 °C: 1.84 (m, H-4, H-5), 3.05-3.1 (m, 5H, H-31, NMe), 3.4 (m, 2H, H-6), 5.86 (d, J = 8Hz, 1H, H-5'), 6.18 (d, J = 6Hz, 1H, H-2'), 6.58 (m, 1H, H-3'), 7.18 (m, 3H, H-6', *o*-phenoxy hydrogens), 7.2 (t, J = 8.5Hz, 1H, *p*-phenoxy hydrogen), 7.35 (m, 5H, phenyl hydrogens), 7.54 (m, 2H, *m*-phenoxy hydrogens). 61 °C: 1.83 (m, H-4, H-5), 3.05-3.1 (m, 5H, NMe, H-3), 3.4 (t, J = 6Hz, 2H, H-6), 5.85 (d, J = 1.5Hz of d, J = 7.5Hz, 1H, H-5'), 6.15 (d, J = 6Hz, 1H, H-2'), 6.54 (d, J = 1Hz of d , J = 1.5Hz of, d, J = 6Hz, 1H, H-3'), 6.9-7.13 (m, 3H, H-6', *o*-phenoxy hydrogens), 7.22.(t, J = 8.5Hz, 1H, *p*-phenoxy

hydrogen), 7.4 (m, 5H, phenyl hydrogens), 7.5 (m, 2H, *m*-phenoxy hydrogens).

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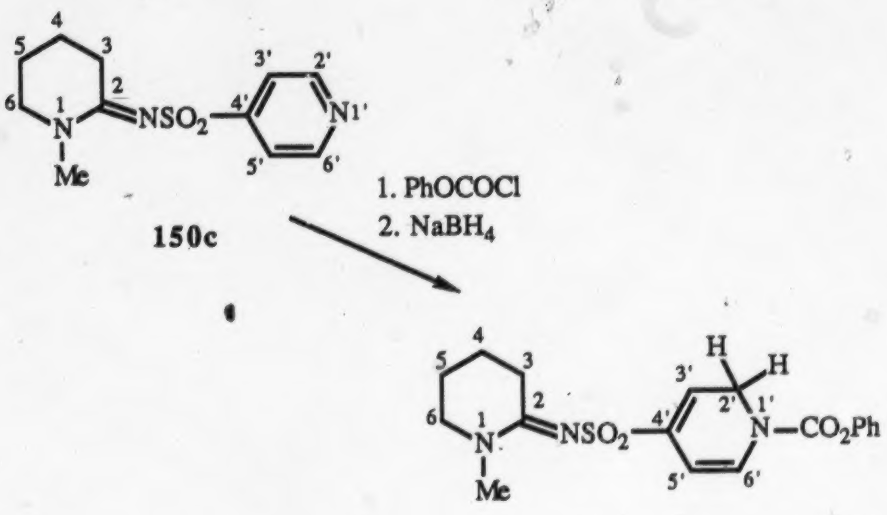
[a] Chemical shift values in square brackets are those for the minor rotameric product.

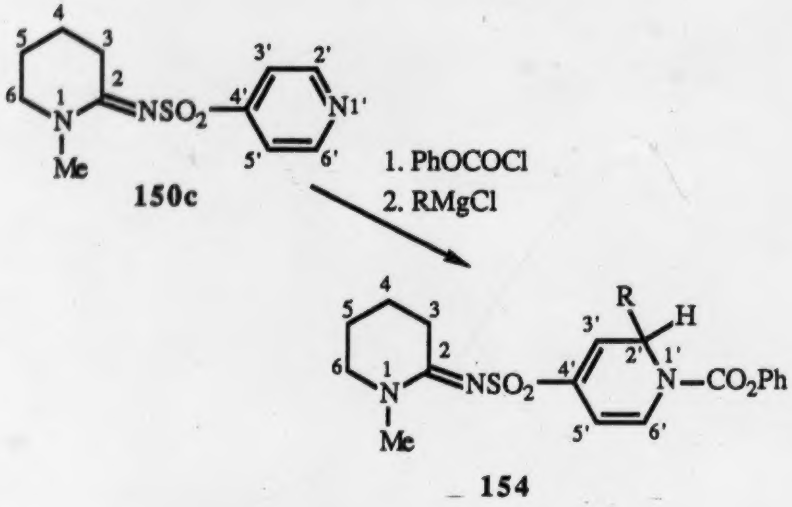


Eq. 22

150c

154a

Treatment of compound **150c** with phenyl chloroformate and a Grignard reagent in a similar manner as described for compound **150b** afforded the 1,2-dihydropyridine products **154b-e** as the sole products (Eq. 23) in chemical yieds of 42 to74% (Table 10). The 1,4-dihydropyridine isomers were not produced because the C-4' position on the pyridine ring is blocked by the sulfonyl substituent.



Eq. 23

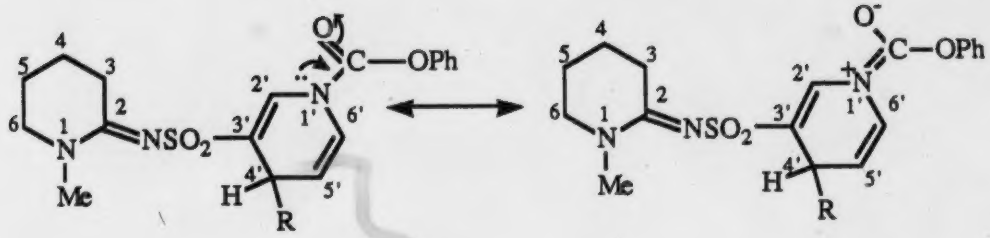
R = Me, *n*-Bu, *t*-Bu, Ph.

IR and ^{1}H NMR spectral data for compounds **154a-e**, summarized in Table 9, are consistent with the assigned structures.

^{1}H NMR variable temperature studies indicated the presence of rotamers in the 1,4- and 1,2-dihydropyridine products **153a-c** and **154a-e** respectively. The rotameric ratios for these compounds at 25 $^\circ$C were as follows: **153a**, 11 : 5; **153b**, 5 : 3; **154a**, 8 : 5; **154b**, 9 : 5; **154c**, 7 : 4; **154d**, 10 : 7. The ^{1}H NMR spectra of compounds **152a-d**, and **153c** did not display clearly separated dual rotameric peaks at 25 $^\circ$C. However the broadening of the H-2' proton for compounds **152a-d** indicated incomplete coalescence at this temperature. The ^{1}H NMR spectrum of compound **153c**, at 61 $^\circ$C exhibited sharper peaks relative to the spectrum at 25 $^\circ$C. Dual resonance peaks usually coalesced at 61 $^\circ$C.

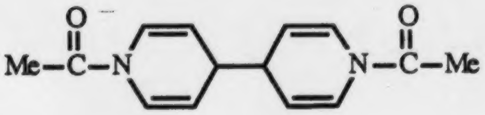
The observed rotational isomerism is the result of restricted rotation about the nitrogen-to-carbonyl bond of the carbamate moiety present in compounds **152-154** as illustrated in Fig. 8 for the 1,4-dihydropyridines (**153**). A similar rotational isomerism attributed to the presence of a carbamate moiety in 4-(dihydropyridine) analogs of nifedepine has been reported.[349] One of the earliest reported observations of rotational isomerism in dihydropyridines was for compound 1,4-dihydropyridine compound

155.[350]



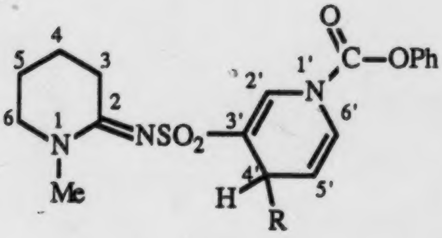
153

Fig. 8: Resonance effect that causes restricted rotation for 1-phenoxycarbonyl-1,4-dihydropyridines (**153**).



155

Compounds **153** and **154** exist in two rotational nitrogen-to-carbonyl configurations **A** , **B** and **C**, **D** respectively. The major rotamer for compounds **154** is likely to have configuration **C** rather than **D**, since it has been reported that the more stable (major) rotamer of a N,N-disubstituted acetamide is usually the rotamer in which the larger substituent of the amide nitrogen is *cis*- to the carbonyl oxygen.[351]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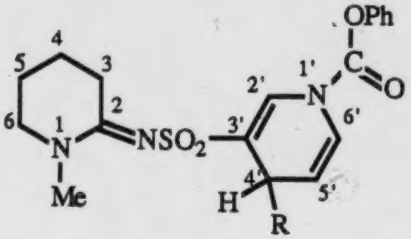
1'
2'
N
6'
5
4
3
2
6
1
N
NSO2
3'
4'
5'
Me
H
R

A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2'
N
6'
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4
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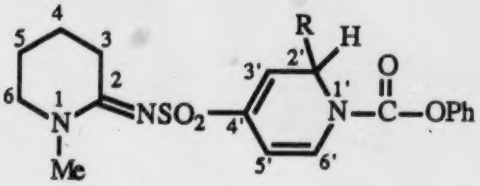
2
6
1
N
NSO2
3'
4'
5'
Me
H
R

B


R
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O
3'
2'
1'
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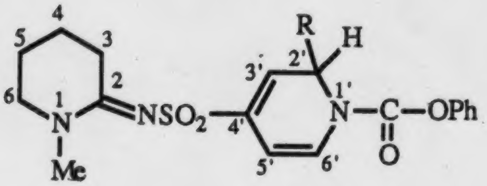
5
4
3
2
6
1
N
NSO2
4'
5'
6'
Me

C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H
3'
2'
1'
N—C—OPh
O
5
4
3
2
6
1
N
NSO2
4'
5'
6'
Me

D

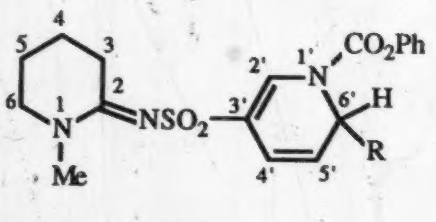
Dual resonances were exhibited primarily by protons on the dihydropyridine ring, i.e. H-2', H-4', H-5' and H-6'. Protons of C-2'(C-4') substituents and the *N*-1 methyl substituent also exhibited dual resonances. The chemical shift difference between dual resonance peaks decreases with increasing distance from the carbamate moiety. For compounds **154a-d** chemical shift differences between dual resonances were: NMe, 0.02 ppm; H-5', 0.03-0.05 ppm range; H-2', 0.4-0.18 ppm range; H-6', 0.06-0.07 ppm range. This observation supports the proposal that the presence of the carbamate moiety in compounds **152-154** gives rise to the observed rotational isomerism. The closer the proton is to the carbamate moiety the greater the separation between dual resonance chemical shifts.

The size, nature and orientation of the R substituent on the dihydropyridine ring, has an influence on the resonance stabilization and the energy barrier to rotation. Large substituents lower the energy barrier to rotation relative to small substituents.[351] This may partly explain the failure of the C-2' phenyl substituted compound (**152e**, R = Ph) to exhibit dual resonace peaks at 25 ^{o}C relative to the C-2' unsubstituted (**152a**, R = H), methyl substituted (**152b**, R = Me), *n*-butyl substituted (**152c**, R = *n*-Bu) and *t*-butyl substituted (**152d**, R = *t*-Bu) compounds. Moreover the Ph substituent is an electron-withdrawing group whereas the Me, *n*-Bu and *t*-Bu substutituents are electron-donating groups. The Ph substituent will therefore , through a negative inductive (-I) effect, lower the C-N π-electron density, thereby lowering the barrier to rotation about the carbon-to-nitrogen bond of the carbamate moiety. The Me, *n*-Bu and *t*-Bu substutituents will exhibit an opposite effect to that of the Ph substutituent.

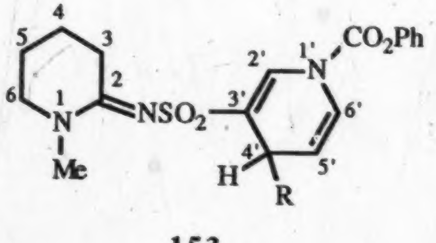
A general observation was made that among these piperidylidene-2-(dihydropyridyl)sulfonamides (**152**-**154**), the relative tendency towards rotational isomerism was **154** (1,2-dihydro-4-pyridyl) > **153** (1,4-dihydro-3-pyridyl) > **152** (1,6-dihydro-3-pyridyl).

A plausible explanation for these differences in tendency towards rotational isomerism can be found in terms of competing delocalization involving the dihydropyridine olefinic bonds and the nitrogen lone-electron pair as illustrated with structures **152 I** and **II**; **153 I** and **II**; **154 I** and **II**, for **152**, **153** and **154**, respectively. This delocalization lowers the barrier to rotation about the nitrogen-to-carbonyl bond. Structure **152 II** will have a greater stability relative to **153 II** because of its higher degree of symmetry. Structure **154 II** will be the least stable because the negative charge is located on a carbon atom , which is less electronegative than an oxygen atom which carries the negative charge in structures **152 II** and **153 II**.

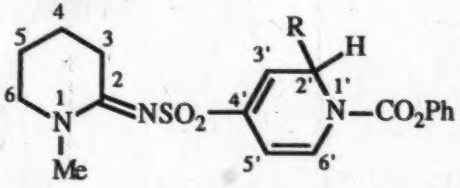
Table 10: Physical and Pharmacological Data for 1-Methylpiperidylidene-2-(dihydropyridine)sulfonamides (**152a-d**, **153a-c** and **154a-e**).



152



153



154

Entry	R	% Yield	MP, °C	Formula	Microanalysis: Calcd.(Found)			Exact Mass		Analgesic Activity[a]
					C	H	N	Calcd.	Found	% Inhibition
152a	Me	42	168-170	$C_{19}H_{23}N_3O_4S$	57.59(57.89)	5.64(5.76)	10.78(10.38)			23.8 ± 6.1
152b	*n*-Bu	50	81-83	$C_{22}H_{29}N_3O_4S$	61.23(60.86)	6.77(6.66)	9.74(9.66)			25.4 ± 4.7
152c	*t*-Bu	56	166-168	$C_{22}H_{29}N_3O_4S$	61.23(60.63)	6.77(6.40)	9.74(9.52)	431.1879	374.1175[b]	33.0 ± 5.7
152d	Ph	87	154-156	$C_{24}H_{25}N_3O_4S$	63.84(63.40)	5.58(5.65)	9.31(9.12)			36.0 ± 8.9
153a	Me	14	oil	$C_{19}H_{23}N_3O_4S$				389.1409	389.1405	NT[c]
153b	*n*-Bu	33	oil	$C_{22}H_{29}N_3O_4S$				431.1879	374.1173[b]	NT
153c	*t*-Bu	32	oil	$C_{22}H_{29}N_3O_4S$				431.1879	374.1177[b]	NT

154a	H	44	141-143	$C_{18}H_{21}N_3O_4S$	57.58(57.63)	5.64(5.35)	11.19(11.01)			inactive
154b	Me	47	oil	$C_{19}H_{23}N_3O_4S$				389.1409	389.1395	36.2 ± 6.0
154c	*n*-Bu	53	oil	$C_{22}H_{29}N_3O_4S$				431.1819	374.1176[b]	28.8 ± 3.7
154d	*t*-Bu	61	188-190	$C_{22}H_{29}N_3O_4S$				431.1819	374.1178[b]	68.8 ± 5.5
154e	Ph	74	150-152	$C_{24}H_{25}N_3O_4S$	63.84(63.46)	5.58(5.64)	9.31(9.27)			inactive
Aspirin[R]										58.0 ± 7.2[d]

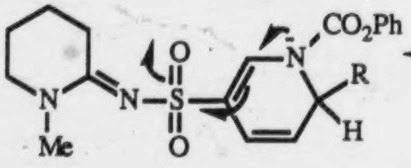
---

[a] Inhibition of 4 % NaCl-induced writhing in rats. The result is the mean ± SEM for five (5) animals.

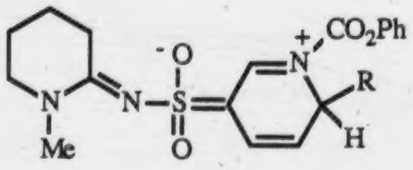
[b] M - C_4H_9 ion.($C_{18}H_{20}N_30_4S$), calculated as 374.1175.

[c] NT = not tested.

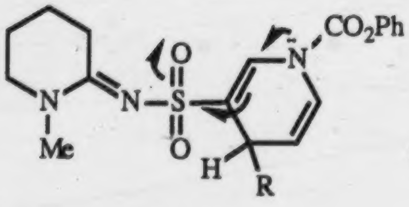
[d] At a dose of 50 mg/kg sc.



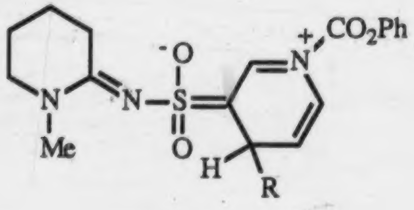
152 I



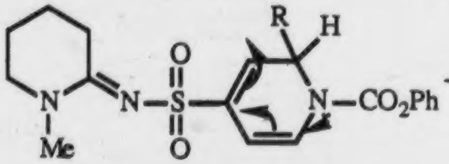
152 II



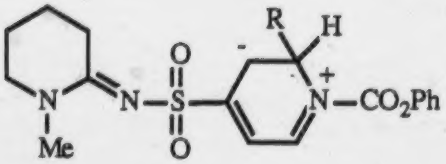
153 I



153 II



154 I



154 II

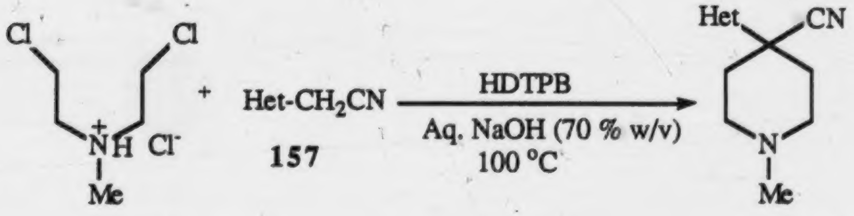
Therefore the barrier to rotation about the nitrogen-to-carbonyl bond will be lowest in compounds **152** and highest in compounds **154**. The higher the energy barrier to rotation the higher the tendency towards rotational isomerism and vice versa.

The H-3' proton of compounds **154** did not exhibit dual resonance peaks at 25 °C in contrast to H-5'. This implies that H-3' may be too remote from the influence of the carbonyl moiety, possibly because of the intervening sp3 C-2' carbon atom, which results in the $C_{2'}$-$N_{1'}$ and $C_{2'}$-$C_{3'}$ bond lengths being longer than those of $C_{6'}$-$N_{1'}$ and $C_{6'}$-$C_{5'}$, respectively. The stereochemistry of the C-2' substituent could also result in shielding of H-3' from the influence of the carbonyl group.

3.2.5.0.0.0. Synthesis of 1-Methyl-4-cyano-4-(pyridyl)piperidines (158a-h)

The new nitriles **158a-h** were synthesized for use as precursors to novel ketobemidone and meperidine analogs **160** and **164**, respectively. Since the classical method [64-66] reported for the synthesis of 4-phenyl-4-cyanopiperidines, which employs sodamide as the condensation agent poses difficulties of amidine formation [352] and dangers of handling sodamide, the facile method developed recently by Cammack and Reeves[353] was used to synthesize **158a-h**. Thus, condensation of the bis-(2-chloroethyl)amine salt **156a** (Eq. 24) or *N*-(2-Chloroethyl)-N-(2-chloropropyl)methylamine hydrochloride **156b** (Eq. 25) with 2-(3- or 4-)-pyridylacetonitrile (**157**), in the presence of excess 70 % w/v aqueous sodium hydroxide and a catalytic quantity of the phase transfer catalyst hexadecyltri-*n*-butylphosphonium bromide (HDTPB) at 100 °C with vigorous stirring, afforded the respective products **158a-h** (Scheme 13). The physical and spectral data for compounds **158a-h** are presented in Tables 11 and 12, respectively. *N*-bis-(2-Chloroethyl)methylamine hydrochloride (**156a**) and *N*-(2-chloroethyl)-*N*-(2-chloropropyl)methylamine hydrochloride (**156b**) were synthesized in 73 and 76 % yield, respectively, by reacting the corresponding alcohols, *N*-

methyldiethanolamine or *N*-(2-hydroxyethyl)-*N*-(2-hydroxypropyl)-*N*-methylamine with thionyl chloride. *N*-(2-Hydroxyethyl)-*N*-(2-hydroxypropyl)-*N*-methylamine was prepared by a new route involving the reaction of 1-bromo-2-propanol with *N*-methylethanolamine.


Cl
Cl
NH Cl⁻
Me
+
Het-CH₂CN
HDTPB
Aq. NaOH (70 % w/v)
100 °C
Het
CN
N
Me

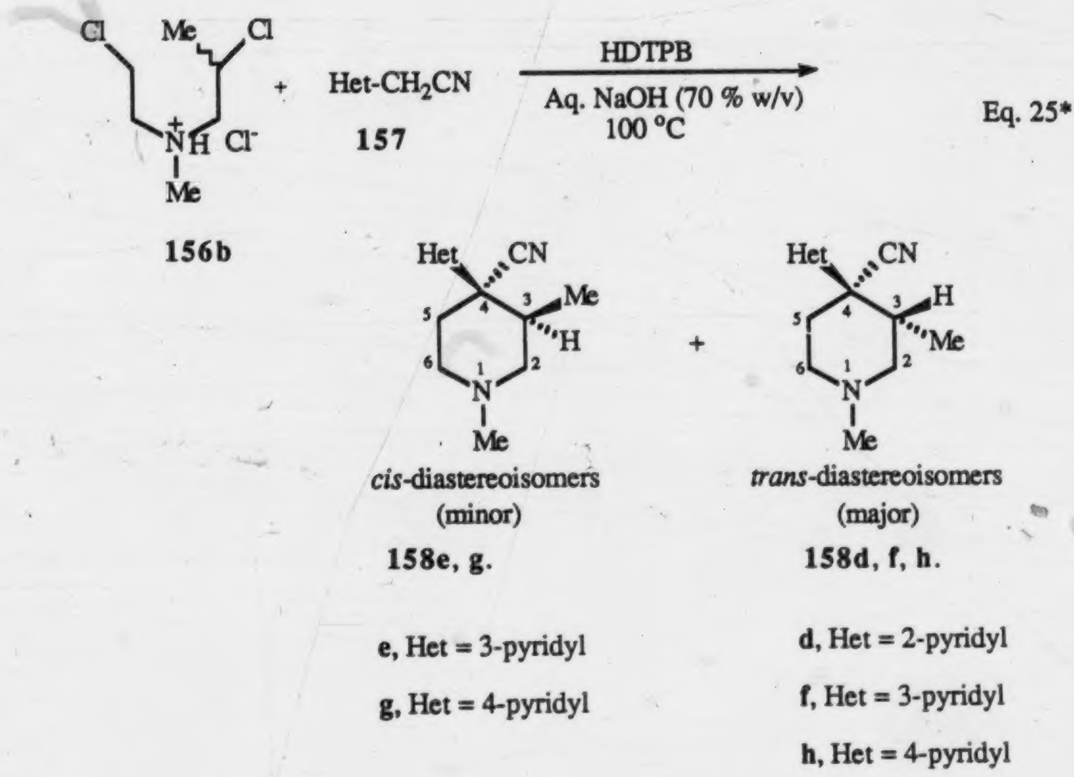
Eq. 24

156a **157** **158**

a, Het = 2-pyridyl

b, Het = 3-pyridyl

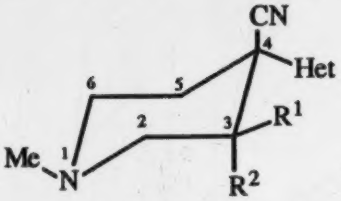
c, Het = 4-pyridyl


Cl
Me
Cl
$\overset{+}{N}H$ Cl⁻
Me
156b
+
Het-CH_2CN
157
HDTPB
Aq. NaOH (70 % w/v)
100 °C
Eq. 25*
Het
CN
Me
H
N
Me
1
2
3
4
5
6
cis-diastereoisomers
(minor)
158e, g.
+
Het
CN
H
Me
N
Me
trans-diastereoisomers
(major)
158d, f, h.
e, Het = 3-pyridyl
g, Het = 4-pyridyl
d, Het = 2-pyridyl
f, Het = 3-pyridyl
h, Het = 4-pyridyl

* Only one enantiomer of each racemic product is represented in Eq. 25

The IR spectra (Table 12) for **158a-h** displayed a characteristic absorption band for the CN substituent at 2237 cm $^{-1}$. The ^{1}H NMR spectra (Table 12) are consistent with the assigned structures. In contrast to the general observation that axial hydrogens on a piperidine ring resonate at higher fields relative to equatorial hydrogens, the C-3(5) axial hydrogens for compound **158a** resonated at δ 2.34, relative to the C-3(5) equatorial hydrogens which resonated at δ 2.16. This deshielding must be due to the point of attachment of the pyridyl ring since the resonances for C-3(5) axial and equatorial protons for **158b-h** overlapped in the δ 2.1-δ 2.26 range. Reaction of **156b** with 2-pyridylacetonitrile afforded only the *trans*-(3-Me/pyridyl)stereoisomer **158d**. The *cis*-(3-Me/pyridyl)stereoisomer (**158**, Het = 2-pyridyl, R^1 = H, R^2 = Me) was not detected, possibly due to very unfavorable nonbonding interactions produced when the 4-(2-pyridyl) ring and the C-3 methyl substituent are *cis*- to each other. Similar reactions employing 3- and 4-pyridylacetonitriles afforded both *cis*- and *trans*-diastereoisomers where the *trans*-stereoisomers (**158e** and **158g**) were the predominate products. The following ratios of *cis*- to *trans*- were observed: **158e** : **158f** = 1 : 5.3; **158g** : **158h** = 1 : 4.2. A similar ratio of *cis*-(3-Me/Ph) to *trans*-(3-Me/Ph)stereoisomers (1 : 3) has been reported for reactions employing benzyl cyanide (phenylacetonitrile) in place of a pyridylacetonitrile.[352] The *cis*- and *trans*- stereoisomeric products were separated by preparative silica gel TLC employing methanol : chloroform (1 : 7 v/v) as development solvent.

Table 11: Physical Data for 1-Methyl-4-cyano-4-(pyridyl)piperidines (**158a-h**).

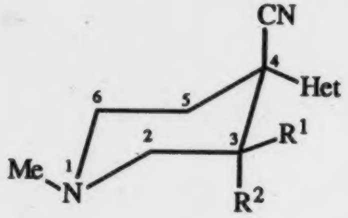


158

Entry	R^1	R^2	Het	% Yield	MP, ^oC	Formula	Microanalysis: Calcd.(Found)			Exact Mass:	
							C	H	N	Calcd.	Found
158a	H	H	2-pyridyl	80	43-44	$C_{12}H_{15}N_3$	71.61(71.31)	7.51(7.57)	20.87(20.67)		
158b	H	H	3-pyridyl	70	65-66	$C_{12}H_{15}N_3$	71.61(71.36)	7.51(7.72)	20.87(20.84)		
158c	H	H	4-pyridyl	58	86-87	$C_{12}H_{15}N_3$	71.61(71.51)	7.51(7.84)	20.87(20.56)		
158d	Me	H	2-pyridyl	85	oil	$C_{13}H_{17}N_3$				215.1423	215.1421
158e	H	Me	3-pyridyl	11	oil	$C_{13}H_{17}N_3$				215.1423	215.1422
158f	Me	H	3-pyridyl	58	oil	$C_{13}H_{17}N_3$	70.27(70.68)	7.87(7.60)	20.87(20.67)[a]		
158g	H	Me	4-pyridyl	12	oil	$C_{13}H_{17}N_3$				215.1423	215.1424
158h	Me	H	4-pyridyl	50	oil	$C_{13}H_{17}N_3$				215.1423	215.1420

[a] Calculated for $C_{13}H_{17}N_3.2^1/_2H_20$

Table 12: IR and ^{1}H NMR Spectral Data for 1-Methyl-4-cyano-4-(pyridyl)piperidines (**158a-h**).



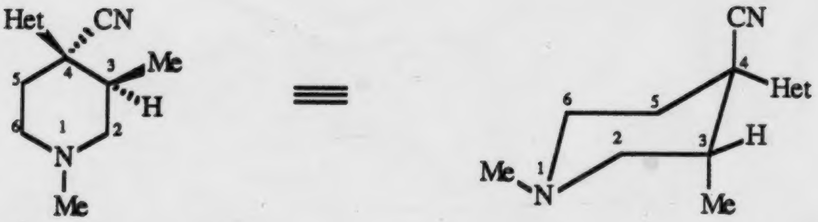
158

Entry	R^1	R^2	Het	IR (CN), cm $^{-1}$	^{1}H NMR ($CDCl_3$), δ
158a	H	H	2-pyridyl	2237	2.16 (d, J = 3Hz of d, J = 4Hz of d, J = 13.2Hz, 2H, H-3eq, H-5eq), 2.34 (d, J = 4Hz of d, J = 12Hz of d, J = 13.2Hz, 2H, H-3ax, H-5ax), 2.4 (s, 3H, NMe), 2.5 (d, J = 4Hz of d, J = 12Hz of d, J = 13Hz, 2H, H-2ax, H-6ax), 3.0 (d, J = 3Hz of d, J = 4Hz of d, J = 13Hz, 2H, H-2eq, H-6eq), 7.3 (d, J = 1.5Hz of d, J = 5Hz of d, J = 8.5Hz, 1H, pyridine H-5), 7.6 (d, J = 1.5Hz of d, J = 8.5Hz, 1H, pyridine H-3), 7.78 (d, J = 1.5Hz of d, J = 8.5Hz of d, J = 8.5Hz, 1H, pyridine H-4), 8.68 (d, J = 1.5Hz of d, J = 5Hz, 1H, pyridine H-6)

158b	H	H	3-pyridyl	2237	2.14-2.26 (m, 4H, H-3eq, H-5eq, H-3ax, H-5ax), 2.42 (s, 3H, NMe), 2.55 (d, J = 5.2Hz of d, J = 10.5Hz of d, J = 12.6Hz, 2H, H-2ax, H-6ax), 3.04 (d, J = 5Hz of d, J = 5Hz of d, J = 12.6Hz, 2H, H-2eq, H-6eq), 7.45 (d, J = 1.5Hz of d, J = 5.3Hz of d, J = 8.5Hz, 1H, pyridine H-5), 7.93 (d, J = 1.5Hz of d, J = 1.5Hz of d, J = 8.5Hz, 1H, pyridine H-4), 8.7 (d, J = 1.5Hz of d, J = 5.3Hz, 1H, pyridine H-6), 8.83 (d, J = 1.5Hz, pyridine H-2).
158c	H	H	4-pyridyl	2237	2.1-2.2 (m, 4H, H-3eq, H-5eq, H-3ax, H-5ax), 2.42 (s, 3H, NMe), 2.5 (d, J = 5.2Hz of d, J = 10.5Hz of d, J = 12.3Hz, 2H, H-2ax, H-6ax), 3.02 (d, J = 3Hz of d, J = 3Hz of d, J = 12.3Hz, 2H, H-2eq, H-6eq), 7.48 (d, J = 2Hz of d, J = 5.5Hz, 2H, pyridine H-3, H-5), 8.72 (d, J = 1Hz of d, J = 5.5Hz,, 2H, pyridine H-2).
158d	Me	H	2-pyridyl	2237	0.78 (d, J = 7.2Hz, 3H, C-3 Me) 2.02 (d, J = 3Hz of d, J = 4Hz of d, J = 12Hz, 1H, H-5eq), 2.18 (d, J = 12Hz of d, J = 14Hz, 1H, H-2ax), 2.38 (s, 3H, NMe), 2.42-2.49 (m, 2H, H-5ax, H-6ax), 2.62 (m, 1H, H-3ax), 2.88 (d, J = 4Hz of d, J = 14Hz, 1H, H-2eq), 2.99 (br d, J = 12Hz, 1H,

					H-6eq), 7.25 (d, J = 1Hz of d, J = 5.5Hz of d, J = 7.5Hz, 1H, pyridine H-5), 7.61 (d, J = 1Hz of d, J = 1.5Hz of d, J = 7.5Hz, 1H, pyridine H-3), 7.74 (d, J = 1.5Hz of d, J = 7.5Hz of d, J = 7.5Hz, 1H, pyridine H-4), 8.63 (d, J = 1Hz of d, J = 1.5Hz of d, J = 5Hz,1H, pyridine H-6).
158e	H	Me	3-pyridyl	2237	0.75 (d, J = 7.5Hz, 3H, C-3 Me), 2.03 (m, 1H, H-5eq), 2.22-2.4 (m, 5H, H-3eq, H-2ax, NMe), 2.42-2.58 (m, 3H, H-5ax, H-2eq, H-6ax), 3.02 (m, 1H, H-6eq), 7.35 (d, J = 1Hz of d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.74 (d, J = 1.5Hz of d, J = 1.5Hz of d, J = 8Hz, 1H, pyridine H-4), 8.61 (d, J = 1.5Hz of d, J = 6Hz, 1H, pyridine H-6), 8.68 (d, J = 1.5Hz, 1H, pyridine H-2).
158f	Me	H	3-pyridyl	2237	0.83 (d, J = 6.75Hz, 3H, C-3 Me), 2.08 (d, J = 3Hz of d, J = 3Hz of d, J = 13.5Hz, 1H, H-5eq), 2.18 - 2.32 (m, 3H, H-5ax, H-2ax, H-3ax), 2.4 (s, 3H, NMe), 2.48 (d, J = 3Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.9 (d, J = 3Hz of d, J = 12Hz, 1H, H-2eq) 2.98 (m, 1H, H-6eq), 7.36 (d, J = 1.5Hz of d, J = 6Hz of d, J = 8.5Hz, 1H, pyridine H-5), 7.84 (d, J = 1.5Hz of d, J = 1.5Hz of d, J = 8.5Hz, 1H, pyridine H-4),

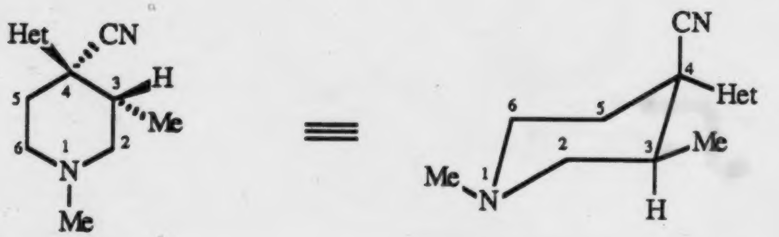
					8.62 (d, J = 1.5Hz of d, J = 6Hz, 1H, pyridine H-6), 8.8 (d, J = 1.5Hz, 1H, pyridine H-2).
158g	H	Me	4-pyridyl	2237	0.8 (d, J = 7.5Hz, 3H, C-3 Me), 1.94 -2.53 (m, 9H, H-5eq, H-5ax, NMe, H-3eq, H-2ax, H-2eq, H-6ax), 3.07 (m, 1H, H-6eq), 7.4 (d, J = 2Hz of d, J = 5.5Hz, 2H, pyridine H-3, H-5), 8.65 (d, J = 2Hz of d, J = 5.5Hz, pyridine H-2, H-6).
158h	Me	H	4-pyridyl	2237	0.83 (d, J = 6.5Hz, 3H, C-3 Me), 2.07 - 2.32 (m, 4H, H-5eq, H-5ax, H-2ax, H-3ax), 2.4 (s, 3H, NMe), 2.47 (m, 1H, H-6ax), 2.9 (m, 1H, H-2eq), 3.0 (m, 1H, H-6eq), 7.38 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.73 (d, J = 2Hz of d, J = 6Hz, pyridine H-2, H-6).



cis-stereoisomer
(minor product)

cis-stereoisomer conformation

158e, g.



trans-stereoisomer
(major product)

trans-stereoisomer conformation

158d, f, h.

Fig. 9: Solution conformations for *cis*- and *trans*- stereoisomers of **158**.

Preferred solution conformations for *cis*- and *trans*-stereoisomers are illustrated in Fig. 9. These conformations were assigned based on the ^{1}H NMR coupling constants (J values) for compounds **158a-h** (Table 12). Proton NMR decoupling experiments performed on the *trans*-diastereoisomers **158d** and **158f**, in which the C-3 methyl group was irradiated, revealed a large ax/ax coupling ($J_{ax,ax}$ = 12Hz) and a small ax/eq coupling ($J_{ax,eq}$ = 4Hz) for H-3. This implies that H-3 of the *trans*-stereoisomers (**158d, f, h**) is axial. Therefore the C-3 methyl group must be equatorial with respect to the piperidine ring (Fig.9).

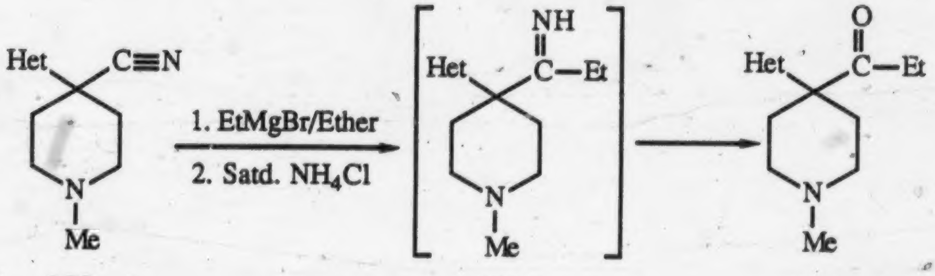
Booth[354] has reviewed the influence which an alkyl substituent on a cyclohexane ring has on the chemical shifts of axial and equatorial ring protons. Eliel *et al*[355] reported that an equatorial methyl substituent exerts a shielding effect of 0.28 ppm on vicinal (β) equatorial protons, whereas an axial methyl substituent exerts a greater shielding effect of 0.4 ppm, in cyclohexanols.

The observed shielding effects of the C-3 methyl substituents of **158d-h** on the C-2 equatorial (β H-2eq) protons as compared with the corresponding 3-unsubstituted analogs **158a-c** were as follows: **158d** (*trans*-), 0.12 ppm; **158e** (*cis*-), 0.46 ppm; **158f** (*trans*-), 0.14 ppm; **158g** (*cis*-), 0.49 ppm; **158h** (*trans*-), 0.12 ppm. These results suggest that the shielding effect of the C-3 methyl substituent on H-2eq is greater in the *cis*-stereoisomers (0.46-0.49 ppm range) relative to the *trans*-stereoisomers (0.12-0.14 ppm range). Correlating these results with the work of Eliel *et al.* [355] leads to the conclusion that the C-3 methyl substituent is axial in the *cis*-stereoisomers **158e** and **158g**, whereas in the *trans*-stereoisomers **158d, f, h** it is equatorial.

In *cis*-stereoisomers, the 3-methyl substituent adopts an axial orientation which places it in a 1,3-diaxial relationship with the piperidine ring nitrogen lone-electron pair, which exerts a shielding effect on it. The C-3 methyl substituent in the *trans*-stereoisomer is therefore deshielded relative to the 3-methyl substituent in the *cis*-stereoisomer which adopts an axial orientation and is more remote from the aromatic ring. Casy *et al* [352] have also proposed similar axial C-3 methyl/equatorial C-4 phenyl and equatorial C-3 methyl/equatorial C-4 phenyl conformations for *cis*- and *trans*-diastereoisomers of 1,3-dimethyl-4-cyano-4-phenylpiperidine, respectively, which are related to compounds **158d-h**.

3.2.5.1.0. Elaboration of nitriles (158) to ketones (160)

The elaboration of nitriles **158a, b, d, e, f** to the corresponding ketones **160a, b, e, f, g** respectively, was undertaken to prepare 4-(pyridinyl) analogs of the opioid analgesic ketobemidone (**11b**). The synthesis of ketones from nitriles via the addition of Grignard reagents to the latter compounds has been reviewed.[356] Ethylmagnesium bromide was added to the nitriles (**158**) in dry ether solution at 25 °C. Two equivalents of the Grignard reagent were used since the 4-cyano group of compounds **158** is highly hindered. The intermediate imine product (**159**) could be hydrolyzed to the ketone (**160**) under mild acidic conditions using saturated ammonium chloride solution for the 3-unsubstituted nitriles **158a-c** (Eq. 26). However, for reactions for which the 3-methyl-substituted nitriles **158d-f** were employed, refluxing with 10 % HCl was required to hydrolyze the corresponding imine intermediates to the ketones. (Scheme 13).



Eq. 26

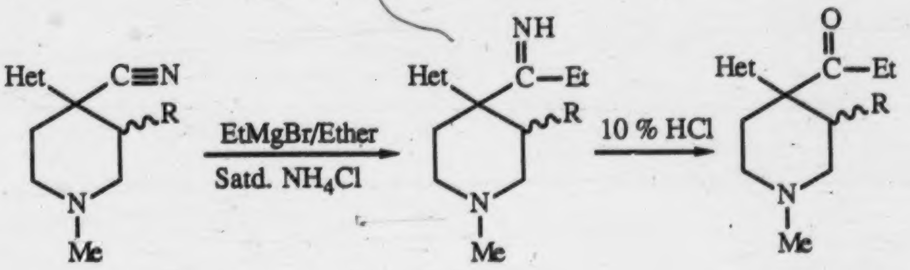
158a, b. **159** **160a, b.**

a, Het = 2-pyridyl

b, Het = 3-pyridyl

a, Het = 2-pyridyl

b, Het = 3-pyridyl



158 **159** **160e, f, g.**

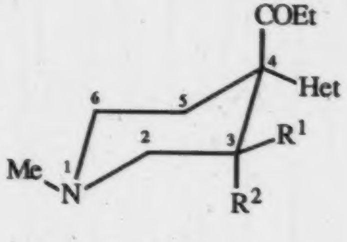
d, R = Me (*trans*-Me/Het),
Het = 2-pyridyl.
e, R = Me (*cis*-Me/Het),
Het = 3-pyridyl.
f, R = Me (*trans*-Me/Het),
Het = 3-pyridyl.

e, R = Me (*trans*-Me/Het),
Het = 2-pyridyl.
f, R = Me (*cis*-Me/Het),
Het = 3-pyridyl.
g, R = Me (*trans*-Me/Het),
Het = 3-pyridyl.

Scheme 13: Reaction sequence for the synthesis of 3-methyl-substituted ketones (**160e-g**).

The mechanism of the addition reaction of Grignard reagents with nitriles has been studied by Swain,[357] and is thought to be a second order reaction. Yields up to 72 % were obtained. However, it has been reported that reaction of Grignard reagents with nitriles is very sensitive to several factors including solvent, temperature and nature of the reagents.The yield obtained is very variable.[356] The 2-pyridinyl nitriles (**158a, 158d**) afforded the corresponding ketones in the highest chemical yields of 65 and 72 % respectively, among the isomeric pyridinyl nitriles used in this study (Table 13).

Table 13: Physical Data for 1-Methyl-4-propionyl-4-(pyridyl)piperidines (160a-h).



160

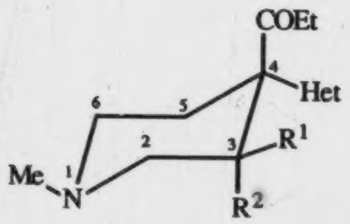
Entry	R^1	R^2	Het	% Yield	MP, °C	Formula	Microanalysis: Calcd.(Found)			Exact Mass:	
							C	H	N	Calcd.	Found
160a	H	H	2-pyr[a]	72	oil	$C_{14}H_{20}N_2O$	72.38(72.34)	8.67(8.51)	12.06(12.21)		
160b	H	H	3-pyr	41	oil	$C_{14}H_{20}N_2O$	72.38(72.52)	8.67(8.68)	12.06(11.96)		
160c	H	H	4-pyr	30	oil	$C_{14}H_{20}N_2O$				232.1576	232.1564
160d	H	Me	2-pyr	65	oil	$C_{15}H_{22}N_2O$				246.1732	246.1731
160e	Me	H	2-pyr	52	oil	$C_{15}H_{22}N_2O$				246.1732	246.1736
160f	H	Me	3-pyr	60	oil	$C_{15}H_{22}N_2O$				246.1732	246.1725
160g	Me	H	3-pyr	33	oil	$C_{15}H_{22}N_2O$				246.1732	246.1732

160h	H	Me	4-pyr	50	oil	$C_{15}H_{22}N_2O$	246.1732	246.1733

---

[a] pyr = pyridyl

Table 14 : IR and ^{1}H NMR Spectral Data for 1-Methyl-4-propionyl-4-(pyridyl)piperidines (**160a-h**).



160

Entry	R^1	R^2	Het	IR (C=O), cm^{-1}	^{1}H NMR ($CDCl_3$), δ
160a	H	H	2-pyridyl	1712	0.9 (t, J = 7.1Hz, 3H, $CH_2\mathit{CH_3}$), 2.24 (s, 3H, NMe), 2.28-2.38 (m, 6H, H-3ax, H-5ax, H-2ax, H-6ax, $\mathit{CH_2}CH_3$), 2.44-2.56 (m, 4H, H-3eq, H-5eq, H-2eq, H-6eq), 7.16 (d, J = 2Hz of d, J = 5Hz of d, J = 8Hz, 1H, pyridine H-5), 7.29 (d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-3), 7.66 (d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.6 (d, J = 2Hz of d, J = 5Hz, 1H, pyridine H-6).

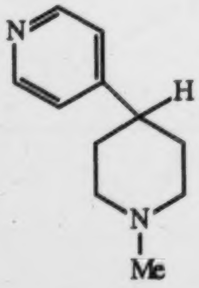
160b	H	H	3-pyridyl	1712	0.9 (t, J = 7.2Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.11 (d, J = 2.2Hz of d, J = 11.8Hz of d, J = 11.8Hz, 2H, H-3ax, H-5ax), 2.2-2.3 (m, 7H, H-2ax, H-6ax, NMe, $\mathit{CH_2}\mathrm{CH_3}$), 2.52 (m, 2H, H-3eq, H-5eq), 2.68 (m, 2H, H-2eq, H-6eq), 7.3 (d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.61 (d,J = 2Hz of d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.52 (d,J = 2Hz of d, J = 6Hz, 1H, pyridine H-6), 8.6 (d,J = 2Hz, 1H, pyridine H-2).
160c	H	H	4-pyridyl	1710	0.9 (t, J = 7.5Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.1 (d, J = 3.5Hz of d, J = 11Hz of d, J = 13Hz, 2H, H-3ax, H-5ax), 2.25 (m, 7H, NMe, $\mathit{CH_2}\mathrm{CH_3}$, H-2ax, H-6ax), 2.48 (m, 2H, H-3eq, H-5eq), 2.61 (d, J = 4Hz of d, J = 4Hz of d, J = 12.5Hz, 2H, H-2eq, H-6eq), 7.22 (d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.6 (d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).
160d	H	Me	2-pyridyl	1704	0.72 (d, J = 7.5Hz, 3H, C-3 Me), 0.8 (t, J = 6.75Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.8 (d, J = 3Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.22 (s, 3H, NMe), 2.25-2.38 (m, 9H, $\mathit{CH_2}\mathrm{CH_3}$, NMe, H-5ax, H-5eq, H-2ax, H-2eq), 2.92-3.02 (m, 2H, H-3eq, H-6eq), 7.16 (d, J = 1.5Hz of d, J =

					6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.2 (d, J = 8Hz, 1H, pyridine H-3), 7.56 (d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.6 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6).
160e	Me	H	2-pyridyl	1704	0.9 (t, J = 7.5Hz, 3H, $\mathrm{CH}_2\mathit{CH}_3$), 1.1 (d, J = 7Hz, 3H, C-3 Me), 2.0 (m, 2H, $\mathit{CH}_2\mathrm{CH}_3$), 2.18 (s, 3H, NMe), 2.2-2.48 (m, 5H, H-3ax, H-5ax, H-5eq, H-2ax, H-6ax), 2.54 (d, J = 4.5 of d, J = 11.3Hz, 2H, H-2eq, H-6eq), 7.17 (d, J = 2Hz of d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.3 (d, J = 8Hz, 1H, pyridine H-3), 7.67 (d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.64 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6).
160f	H	Me	3-pyridyl	1704	0.74 (d, J = 7.5Hz, 3H, C-3 Me), 0.9 (t, J = 7Hz, 3H, $\mathrm{CH}_2\mathit{CH}_3$), 1.86 (d, J = 3.8Hz, of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.18-2.3 (m, 5H, NMe, $\mathit{CH}_2\mathrm{CH}_3$), 2.34 (d, J = 2.3Hz of d, J = 12Hz, 1H, H-2ax), 2.42-2.47 (m, 2H, H-5ax, H-5eq), 2.6 (d, J = 2Hz, of d, J = 2Hz of d, J = 12Hz, 1H, H-2eq), 2.9 (m, 1H, H-3eq), 2.98.(m, 1H, H-6eq), 7.28. (d, J = 1Hz of d, J = 6Hz of d, J = 8Hz, 1H, pyridine

					H-5), 7.53 (d, J = 1.5Hz of d, J = 1.5Hz of d, J = 8Hz, 1H, pyridine H-4), 8.56 (m, 2H, pyridine H-2, H-6).
160g	Me	H	3-pyridyl	1704	0.9 (t, J = 7.5Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.14 (d, J = 6.5Hz, 3H, C-3 Me), 2.06 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 2.2 (s, 3H, NMe), 2.3-2.62 (m, 7H, H-3ax, H-5ax, H-5eq, H-2ax, H-6ax, H-2eq, H-6eq), 7.32 (d, J = 5Hz, of d, J = 8Hz, 1H, pyridine H-5), 7.64 (d, J = 1.5Hz of d, J = 1.5Hz of d, J = 8Hz, 1H, pyridine H-4), 8.54 (d, J = 1.5Hz of d, J = 5Hz, 1H, pyridine H-6), 8.65 (d, J = 1.5Hz, 1H, pyridine H-2).
160h	H	Me	4-pyridyl	1704	0.7 (d, J = 7.5Hz, 3H, C-3 Me), 0.85 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.82 (d, J = 3Hz, of d, J = 12.2Hz of d, J = 12.2Hz, 1H, H-6ax), 2.12-2.47 (m, 8H, $\mathit{CH_2}\mathrm{CH_3}$, NMe, H-2ax, H-5eq, H-5ax), 2.58 (d, J = 2Hz of d, J = 12Hz, 1H, H-2eq), 2.85 (m, 1H, H-3eq), 2.98 (m, 1H, H-6eq), 7.14

(d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.55 (d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).

Reaction of the 4-pyridinyl nitriles **158c, g, h** with ethylmagnesium bromide gave predominantly the descyano products.Thus compound **158c** afforded the descyano product (**161**) and the desired ketone (**160c**) in 61 and 10 % chemical yields respectively, upon treatment with ethylmagnesium bromide in dry ether at 25 ^{o}C followed by hydrolysis. These products were separated by silica gel TLC using MeOH : $CHCl_3$, 1 : 1 v/v, as development solvent . The Rf values of **160c** and **161** were 0.35 and 0.3 respectively. A similar reaction of the 3-methyl-4-cyano-4-(4-pyridyl)piperidines **158g, h** with ethylmagnesium bromide afforded mixtures of products which did not contain the desired ketone products.



161

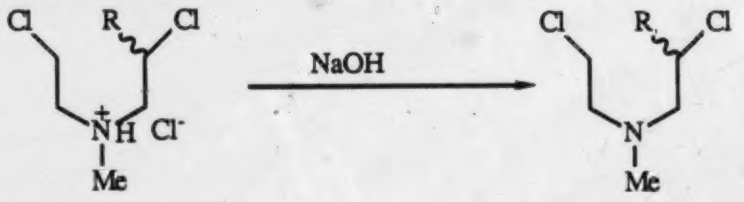
It has been reported that Grignard reagents can cleave cyano groups of some nitriles in a similar manner to sodamide (a reason why sodamide was not used as a base in the condensation reactions of 2-, 3- and 4-pyridylacetonitrile with the chloroethylamine salts **156a,b** to synthesize the nitriles **158**), resulting in the replacement of the cyano group by a hydrogen atom.[358] The 4-pyridinyl ketones **160c,h** were therefore synthesized by addition of ethylmagnesium bromide to the corresponding esters **164c,k**. This reaction was conducted in THF at 0 ^{o}C and at refluxing temperature with **164c** and **164k**, respectively. Steric hindrance at the ester carbonyl of compounds **164** makes it difficult for a second molecule of Grignard reagent to react with the ketone formed by initial reaction of the Grignard reagent with the ester substituent. A similar reaction of the *trans*-3-methyl-4-(4-pyridinyl)piperidine ester **164l** with ethylmagnesium *trans*-3-methyl-4-(4-pyridinyl)piperidine ester **164l** with ethylmagnesium bromide in THF under reflux resulted in a mixture of products (not characterized) from which the desired ketone was absent.

The IR spectra (Table 14) for compounds **160** displayed a strong carbonyl absorption band in the 1704-1712 cm^{-1} range. Introduction of a C-3 methyl substituent shifted the carbonyl absorption frequency from the 1710-1712 cm^{-1} range (compounds **160a-c**) to 1704 cm^{-1} (compounds **160d-h**).The reason for a shift to lower IR absorption frequency is likely due to the electron donating effect of the 3-methyl substituent.

The ^1H NMR spectral data for compounds **160a-h** are presented in Table 14. The 3-methyl resonance for the *cis* -stereoisomers appeared as a doublet at higher field (δ 0.7 - 0.74 range) than the 3-methyl signal for the *trans* -stereoisomers (δ 1.1- 1.14 range). A similar difference between the C-3 methyl resonances of *cis*- and *trans*- 3-methylpethidine derivatives has been reported.[352] The difference in chemical shifts for the C-3 methyl substituents of the *trans*- and *cis*-stereoisomers is more pronounced for the ketones (**160**; - 0.38 - 0.4 ppm range) than for the nitriles (**158**; 0.03 - 0.04 ppm range). This may be due to different shielding and/or steric effects for the propionyl group relative to the cyano group. The increased strain could create a difference in the chemical environments for the 3-methyl substituents of the *cis*- and *trans*-stereoisomers.The propionyl substituent could force the aromatic group to be oriented closer to the the axial 3-methyl substituent for the *cis*-stereoisomer. This would result in a greater degree of shielding for the 3-methyl substituent of the ketones (0.05 - 0.1 ppm range) relative to the chemical shift of the C-3 Me of the corresponding nitrile. In the *trans*- stereoisomer the 3-methyl substituent is equatorial and oriented closer to the carbonyl group. It is therefore deshielded by the paramagnetic anisotropic effect of the carbonyl group.

3.2.6.0.0.0. Synthesis of 4-Ethoxycarbonyl-1-methyl-4-(pyridyl)piperidines (164a-n)

4-Ethoxycarbonyl-1-methyl-4-phenylpiperidines (meperidine and its derivatives) have been synthesized by the ethanolysis of 4-cyano-1-methyl-4-phenylpiperidines.[66] However this method can result in decyanation, and involves sealed tube reactions. The one step condensation of the nitrogen mustards **162** with ethyl 2-, 3- or 4-pyridyl acetate **163a-c** was therefore employed to synthesize compounds **164a-n** .



Eq. 27

156

a, R = H

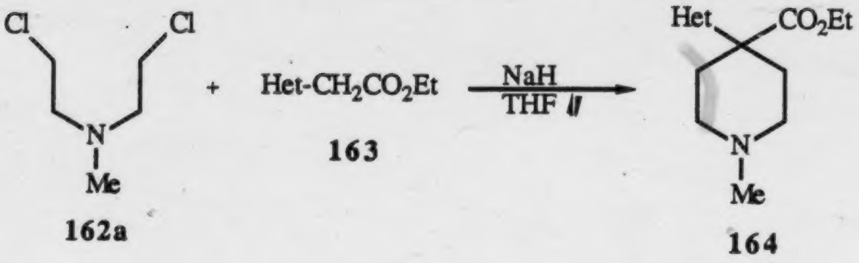
b, R = Me

162

a, R = H

b, R = Me

The electron withdrawing effect of the pyridine ring and ester group facilitated hydrogen abstraction from the active methylene moiety of acetates **163**. Therefore sodium hydride, a milder and less dangerous base than sodamide,[66] was used as the base. The reaction was conducted in refluxing THF. Chemical yields of 50-65% (Table 15) were obtained for the C-3-unsubstituted compounds (**164a-c**) when mechlorethamine (**162a**) was used (Eq.28).


Cl
Cl
N
Me
162a
+
Het-CH$_2$CO$_2$Et
163
NaH
THF Δ
Het
CO$_2$Et
N
Me
164

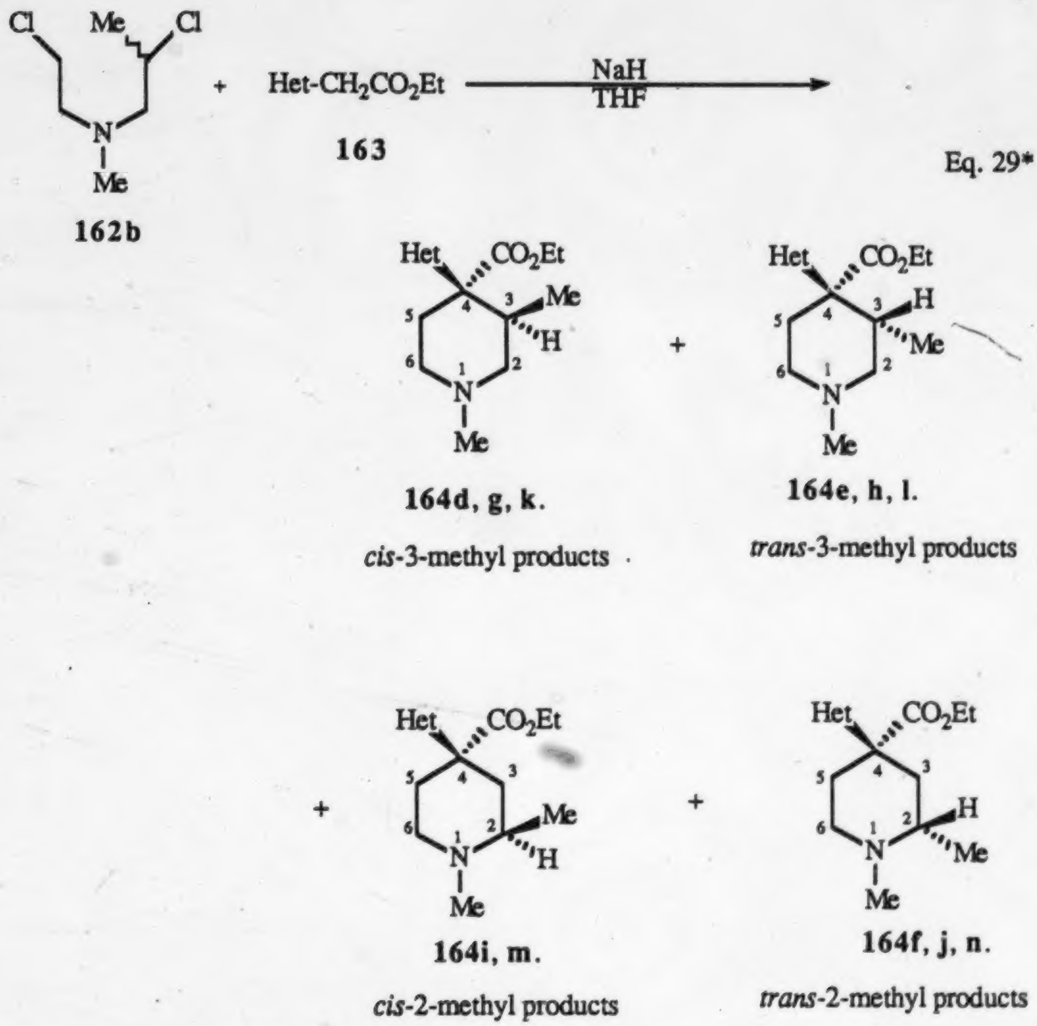
Eq. 28

a, Het = 2-pyridyl

b, Het = 3-pyridyl

c, Het = 4-pyridyl

However reactions employing the unsymmetrical nitrogen mustard (**162b**) afforded mixtures of the expected *cis*- (3-Me/pyridyl, **164d**, **g**, **k**) and *trans*- (3-Me/pyridyl, **164e**, **h**, **l**), as well as the unexpected *cis*- (2-Me/pyridyl, **164i**, **m**) and *trans*- (2-Me/pyridyl, **164f**, **j**, **n**) diastereoisomers in low yields (Eq.29).



Eq. 29*

164d, g, k.

cis-3-methyl products

164e, h, l.

trans-3-methyl products

164i, m.

cis-2-methyl products

164f, j, n.

trans-2-methyl products

*Only one enantiomer of each racemate is shown in Eq. 29

The total yields for the isomeric pyridinyl compounds were: 2-pyridinyl 30%, 3-pyridinyl 29% and 4-pyridinyl 34%. The diastereoisomers were separated by TLC (silica gel, MeOH : $CHCl_3$, 1 : 7 v/v) and their Rf values are given in Table 15. The Rf values for the *trans*-3-methyl-4-(2-pyridinyl) and *trans*-2-methyl-4-(2-pyridinyl) compounds **164e** (0.56) and **164f** (0.58), respectively, were so close that they could not be separated by the above method. The yields (2% each) of the *cis*-2-methyl diastereoisomers **164i** and **164m** were so small and their Rf values, 0.52 and 0.49, respectively, were so close to those of their respective *trans-* isomers **164l** (Rf = 0.55) and **164m** (Rf = 0.51) that they could not be separated pure from these *trans-* isomers.

The unexpected formation of the C-2 methyl compounds **164f, i, j, m** and **n** can be explained by invoking an unsymmetrical aziridinium intermediate **165** in the reaction mechanism (Fig 10). A similar involvement of an unsymmetrical aziridinium ion intermediate has been used to explain the formation of isomethadone in addition to methadone in the synthesis of the latter compound.[359] The involvement of an unsymmetrical aziridinium ion in reactions leading to isomeric products is referred to as the cycloammonium rearrangement.[171]

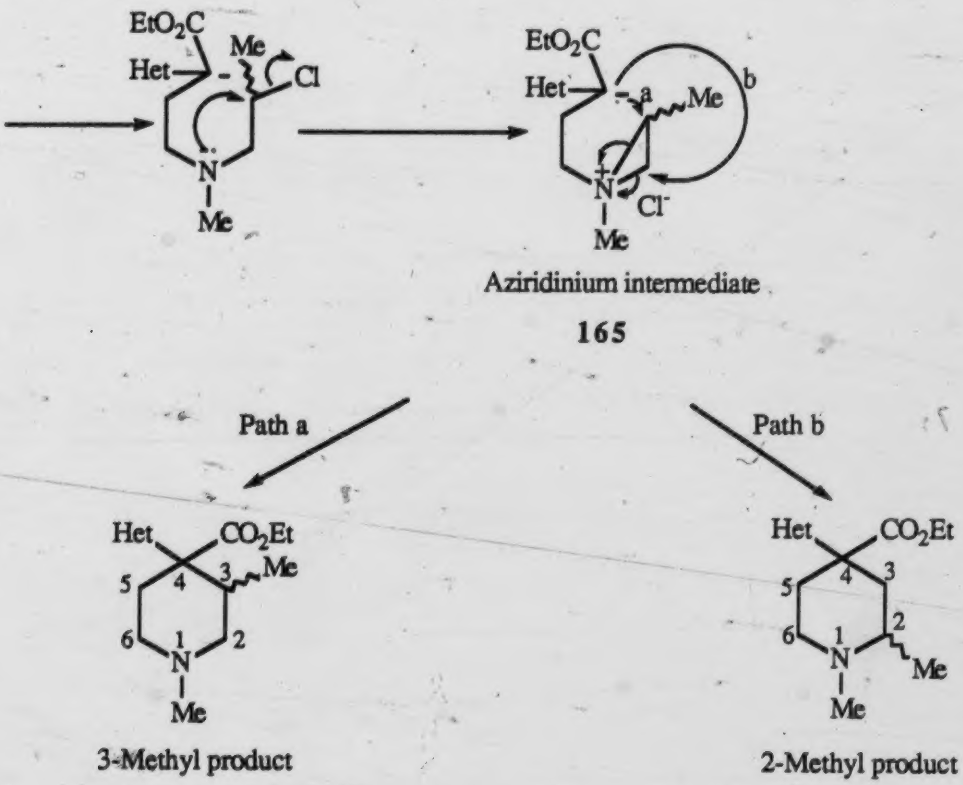

EtO$_2$C
Het
Me
Cl
N
Me
EtO$_2$C
Het
a
Me
b
N
Cl$^-$
Me
Aziridinium intermediate
165
Path a
Path b
Het
CO$_2$Et
Me
5
4
3
6
1
2
N
Me
3-Methyl product
Het
CO$_2$Et
5
4
3
2
6
1
N
Me
Me
2-Methyl product

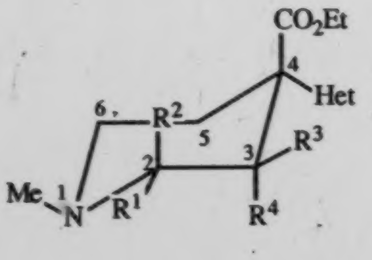
Fig 10: Mechanism leading to isomeric 2-methyl and 3-methyl products

The fact that these reactions afforded a higher yield of the 3-methyl relative to the 2-methyl isomers (2-pyridyl, 14 : 5; 3-pyridyl, 11: 5; 4-pyridyl, 2.1 : 1) suggests that the 3-methyl isomer was produced , at least in part, by direct nucleophilic displacement of chlorine. If the aziridinium intermediate pathway was the only mechanism for the formation of the 3-methyl isomers, the 2-methyl product would be expected to predominate over the 3-methyl isomer since pathway b , which involves an S_N2 displacement at a secondary carbon atom should be more facile than pathway a , which involves an S_N2 reaction at a tertiary carbon atom.

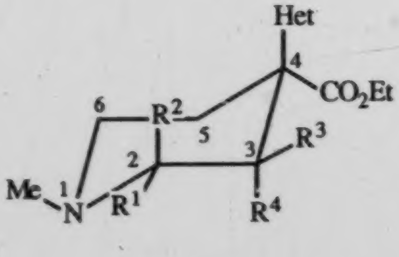
The IR absorption frequencies for the ester carbonyl (C=O) group of compounds **164a-n**, which are presented in Table 16, appear in the 1720-1729 cm^{-1} range.The structures of compounds **164** were established using ^{1}H (Table 16), ^{13}C (Table 17) and two dimensional heteronuclear shift correlated NMR spectrometry (Fig. 11 and Fig. 12). Comparison with previously established structural and stereochemical assignments reported for related 2-methyl and 3-methyl *cis*- and *trans*-diastereoisomers of 1,2(and 1,3)-dimethyl-4-phenyl-4-piperidinol esters[360-362] also facilitated these assignments. The proposed solution conformations adopted by *cis*- and *trans*-diastereoisomers for 2-methyl and 3-methyl compounds are shown in Fig. 13.

The ^{1}H NMR spectra of the *cis*-(3-methyl/pyridyl)stereoisomers (**164d, g, k**) display a C-3 Me signal upfield (δ 0.7-0.8 range) of the C-3 Me chemical shift (δ 1.06-1.1 range) for the corresponding *trans*-(3-methyl/pyridyl)stereoisomers (**164e, h, l**).This difference is attributed to the fact that the C-3 methyl group of the *cis*- isomers, being in an axial orientation, is less affected by the deshielding anisotropic effect of the C-4 ester carbonyl than the C-3 methyl substituent of the *trans*- isomers which is equatorial. The narrow width (width at half height = 16-18Hz range) of the H-3 resonance of the *cis*-stereoisomers (**164d, g, k**) indicates that H-3 of these *cis*-isomers (**164d, g, k**) is equatorial (absence of ax/ax coupling). The ^{13}C NMR signal for the C-3 Me (δ 14.84) of the *cis*-isomer compound **164g** was at a higher field than the C-3 Me signal (δ 15.18) of the corresponding *trans*- isomer **164h**, indicating that the C-3 Me of the *cis*- isomer **164g** is axial whereas that of the *trans*- isomer **164h** is equatorial. The upfield position of the C-5 chemical shift of compound **164g** (δ 26.33) compared to the chemical shift position of C-5 of the *trans*-stereoisomer **164h** (δ 29.58) implies that the C-3 axial methyl substituent of compound **164g** is exerting a γ-shielding effect (6.94 ppm) on the C-5 carbon atom. An axial 3-methyl substituent on the piperidine ring of 4-phenylpiperidines exerts a γ-shielding effect of about 7.9 ppm, whereas an equatorial 3-methyl substituent exerts a smaller γ-shielding effect of 2.9 ppm.[361]

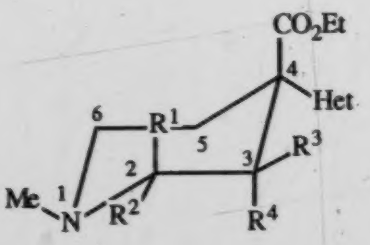
Table 15: Physical Data for 1-Methyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (164a-n)[a]


CO$_2$Et
4
Het
6
R^2
5
R^3
3
2
Me
1
N
R^1
R^4

164a-e, g, h, k, l.


Het
4
CO$_2$Et
6
R^2
5
R^3
3
2
Me
1
N
R^1
R^4

164f, j, n.


CO$_2$Et
4
Het
6
R^1
5
R^3
3
2
Me
1
N
R^2
R^4

164i, m.

Entry	R^1	R^2	R^3	R^4	Het	% Yield	MP, °C	Formula	Microanalysis: Calcd.(Found)			Exact Mass: Calcd.(Found)
									C	H	N	
164a	H	H	H	H	2-pyr[b]	55	oil	$C_{14}H_{20}N_2O_2$	67.72(67.77)	8.12(8.06)	11.28(11.14)	
164b	H	H	H	H	3-pyr	50	36-37	$C_{14}H_{20}N_2O_2$	67.72(67.58)	8.12(8.12)	11.28(11.14)	
164c	H	H	H	H	4-pyr	65	47-49	$C_{14}H_{20}N_2O_2$	67.72(68.02)	8.12(8.19)	11.28(11.38)	
164d	H	H	H	Me	2-pyr	7.5	oil	$C_{15}H_{22}N_2O_2$				262.1681(262.1677)
164e	H	H	Me	H	2-pyr	15[c]	oil	$C_{15}H_{22}N_2O_2$		ND[d]		ND
164f	Me	H	H	H	2-pyr	8[c]	oil	$C_{15}H_{22}N_2O_2$		ND		ND
164g	H	H	H	Me	3-pyr	9	oil	$C_{15}H_{22}N_2O_2$	26.10(26.10)	3.21(3.29)	4.06(4.12)[e]	

164h	H	H	Me	H	3-pyr	10.5	oil	$C_{15}H_{22}N_2O_2$	27.55(27.70)	3.60(3.50)	4.17(4.33)[f]	
164i	H	Me	H	H	3-pyr	2[c]	oil	$C_{15}H_{22}N_2O_2$		ND		ND
164j	Me	H	H	H	3-pyr	7	oil	$C_{15}H_{22}N_2O_2$				262.1681(262.1678)
164k	H	H	H	Me	4-pyr	8.3	oil	$C_{15}H_{22}N_2O_2$	27.55(27.70)	3.60(3.49)	4.17(4.23)[f]	
164l	H	H	Me	H	4-pyr	15.0	oil	$C_{15}H_{22}N_2O_2$				262.1681(262.1662)
164m	H	Me	H	H	4-pyr	2[c]	oil	$C_{15}H_{22}N_2O_2$		ND		ND
164n	Me	H	H	H	4-pyr	9	oil	$C_{15}H_{22}N_2O_2$	53.72(53.37)	7.21(7.41)	8.35(8.34)[g]	

---

[a] Rf values are: **164a** (0.38), **164b** (0.33), **164c** (0.31), **164d** (0.67), **164e** (0.56), **164f** (0.58), **164g** (0.63), **164h** (0.42), **164i** (0.51), **164j** (0.55), **164k**(0.63), **164l** (0.40), **164m** (0.49), **164n** (0.51). System for **164a-c** was silica gel, MeOH : $CHCl_3$ = 1 : 1 v/v, whereas the system for **164d-n** was silica gel, MeOH : $CHCl_3$ = 1 : 7 v/v.

[b] pyr = pyridyl.

[c] Calculated from ^{1}H NMR integrals for ester methylene ($\mathit{CH_2}CH_3$) quartet.

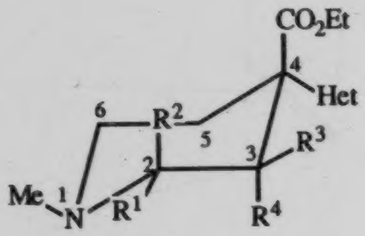
[d] ND = Not determined.

[e] Calculated for $C_{15}H_{24}N_2O_2Cl_6Pt.H_2O$.

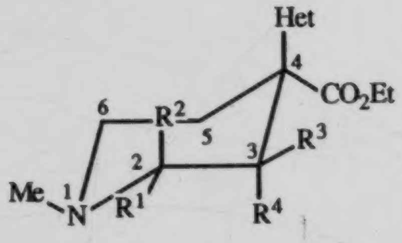
[f] $C_{15}H_{24}N_2O_2Cl_6Pt$.

[g] Calculated for dihydrochloride salt ($C_{15}H_{22}N_2O_2.2HCl$).

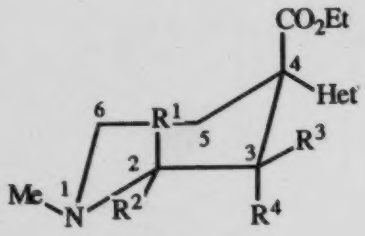
Table 16: IR and ^{1}H NMR Spectral Data for 1-Methyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (**164a-n**).


CO2Et
Het
R2
R3
R1
R4
Me
N
1
2
3
4
5
6

164a-e, g, h, k, l.


Het
CO2Et
R2
R3
R1
R4
Me
N
1
2
3
4
5
6

164f, j, n.


CO2Et
Het
R1
R3
R2
R4
Me
N
1
2
3
4
5
6

164i, m.

Entry	R^1	R^2	R^3	R^4	Het	IR (C=O), cm^{-1}	^{1}H NMR (CDCl$_3$), δ:
164a	H	H	H	H	2-pyridyl	1720	1.16 (t, J = 7.3Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.1-2.32 (m, 7H, H-3ax, H-5ax, H-2ax, H-6ax, NMe), 2.54 (br d, J = 12.2Hz, 2H, H-3eq, H-5eq), 2.73 (m, 2H, H-2eq, H-6eq), 4.15 (q, J = 7.3Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.13 (d, J = 1Hz of d, J = 5Hz of d, J = 8Hz, 1H, pyridine H-5), 7.34 (d, J = 8Hz, 1H, pyridine H-3), 7.64 (d, J = 1.5Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.54 (d, J = 1.5Hz of d, J = 5Hz, 1H, pyridine H-6).

164b	H	H	H	H	3-pyridyl	1729	1.2 (t, J = 7Hz, 3H, $\mathrm{CH_2}CH_3$), 1.9 (d, J = 12Hz, of d, J = 12Hz, 2H, H-3ax, H-5ax), 2.16 (d, J = 12Hz, of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.26 (s, 3H, NMe), 2.64 (d, J = 12Hz, 2H, H-3eq, H-5eq), 2.8 (d, J = 12Hz, 2H, H-2eq, H-6eq),. 4.2 (q, J = 7Hz, 2H, $CH_2\mathrm{CH_3}$), 7.3 (d, J = 5.5Hz of d, J = 8Hz, 1H, pyridine H-5), 7.75 (d, J = 1.6Hz of d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.55 (d, J = 2Hz of d, J = 5.5Hz, 1H, pyridine H-6), 8.72 (d, J = 1.6Hz, 1H, pyridine H-2).
164c	H	H	H	H	4-pyridyl	1728	1.2 (t, J = 6.8Hz, 3H, $\mathrm{CH_2}CH_3$), 1.96 (d, J = 2Hz of d, J = 12Hz of d, J = 12.6Hz, 2H, H-3ax, H-5ax), 2.16(d, J = 11.4Hz of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.28 (s, 3H, NMe), 2.54 (d, J = 2Hz of d, J = 2.4Hz of d, J = 12.6Hz, 2H; H-3eq, H-5eq), 2.78 (d, J = 2Hz of d, J = 2Hz of d, J = 11.4Hz, 2H, H-2eq, H-6eq), 4.16 (q, J = 6.8Hz, 2H, $CH_2\mathrm{CH_3}$), 7.3 (d, J = 2Hz of d, J = 5.5Hz, 2H, pyridine H-3, H-5), 8.59 (d, J = 2Hz of d J = 5.5Hz, 2H, pyridine H-2, H-6).

164d	H	H	H	Me	2-pyridyl	1729	0.74 (d, J = 7Hz, 3H, C-3 Me), 1.15 (t, J = 7.2Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.96 (d, J = 3Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.25 (s, 3H, NMe), 2.36-2.52 (m, 3H, H-5ax, H-5eq, H-2ax), 2.66 (d, J = 2Hz of d J = 2Hz of d, J = 12Hz, 1H, H-2eq), 2.95 (m, 2H, H-3eq, H-6eq), 4.08-4.22 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.14 (d, J = 1.5Hz of d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.33 (d, J = 8Hz, 1H, pyridine H-3), 7.65(d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.58 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6).
164e	H	H	Me	H	2-pyridyl[a]	1729	1.06 (d, J = 6.5Hz, 3H, C-3 Me), 1.22 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.2-2.6 (m, 10H, NMe, H-2ax, H-2eq, H-3ax, H-5ax, H-5eq, H-6ax, H-6eq), 4.08 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.14 (m, 1H, pyridine H-5), 7.33 (d, J = 7.5Hz, 1H, pyridine H-3), 7.65 (m, 1H, pyridine H-4), 8.64 (d, J = 1Hz of d, J = 1.5Hz of d, J = 6Hz, 1H, pyridine H-6).

164f	Me	H	H	H	2-pyridyl[a]	1729	1.22 (m, 6H, C-2 Me, $\mathrm{CH_2}CH_3$), 1.92 (d, J = 12.2Hz of d, J = 12.2Hz, 1H, H-3ax), 2.0 (m, 1H, H-2), 2.1 (m, 1H, H-6ax), 2.2 (s, 3H, NMe), 4.2 (q, J = 7Hz, 2H, $CH_2\mathrm{CH_3}$), 7.14 (m, 1H, pyridine H-5), 7.33 (d, J = 8Hz, 1H, pyridine H-3), 7.65 (m, 1H, pyridine H-4), 8.58 (d, J = 6Hz, 1H, pyridine H-6).
164g	H	H	H	Me	3-pyridyl	1720	0.8 (d, J = 7Hz, 3H, C-3 Me), 1.18 (t, J = 7Hz, 3H, $\mathrm{CH_2}CH_3$), 1.9 (d, J = 3Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.24 (m, 4H, NMe, H-5ax), 2.28 (d, J = 4Hz of d, J = 11.5Hz, 1H, H-2ax), 2.54 (d, J = 2Hz of d, J = 4Hz of d, J = 12.2Hz, 1H, H-5eq), 2.7 (d, J = 11.5Hz, 1H, H-2eq), 2.9 - 3.0 (m, 2H, H-3eq, H-6eq), 4.06-4.2 (m, 2H, $CH_2\mathrm{CH_3}$), 7.26 (d, J = 5Hz of d, J = 8Hz, 1H, pyridine H-5), 7.68 (d, J = 2Hz of d, J = 2Hz of d, J = 8.5Hz, 1H, pyridine H-4), 8.5 (d, J = 2Hz of d, J = 5Hz, 1H, pyridine H-6), 8.63 (d, J = 2Hz, 1H, pyridine H-2).

164h	H	H	Me	H	3-pyridyl	1729	1.1 (d, J = 6.6Hz, 3H, C-3 Me), 1.23 (t, J = 7.2Hz, 3H, CH_2CH_3), 2.2-2.6 (m, 10H, NMe, H-3ax, H-2ax, H-2eq, H-5ax, H-5eq, H-6ax, H-6eq), 4.19 (q, J = 7.2Hz, 2H, CH_2CH_3), 7.28 (d, J = 5.5Hz of d, J = 8Hz, 1H, pyridine H-5), 7.62 (d, J = 8Hz, 1H, pyridine H-4), 8.5 (d, J = 1.5Hz of d, J = 5.5Hz, 1H, pyridine H-6), 8.57 (d, J = 2Hz, 1H, pyridine H-2).
164i	H	Me	H	H	3-pyridyl^b	1729	1.18-1.24 (m, 6H, C-2 Me, CH_2CH_3), 1.55 (d, J = 11Hz of d, J = 13Hz, 1H, H-3ax), 1.95-2.0 (d, J = 4Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-5ax), 2.08 (m, 1H, H-2ax), 2.24 (d, J = 2Hz of d, J = 12Hz of d, J = 13Hz, 1H, H-6ax), 2.28 (s, 3H, NMe), 2.58 (d, J = 2Hz of d, J = 13Hz, 1H, H-3eq), 2.66 (d, J = 3Hz of d, J = 3Hz of d, J = 12Hz, 1H, H-5eq), 2.95 (d, J = 3Hz of d, J = 3Hz of d, J = 13Hz, 1H, H-6eq), 4.12 (q, J = 7.2Hz, 2H, CH_2CH_3), 7.24 (d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.68 (d, J = 2Hz of d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.48 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6), 8.65 (d, J = 2Hz, 1H, pyridine H-2).

164j	Me	H	H	H	3-pyridyl	1729	1.15 (m, 6H, C-2 Me, $\mathrm{CH_2}\mathit{CH_3}$), 1.92 (d, J = 12Hz of d, J = 12Hz, 1H, H-3ax), 2.0 (m, 1H, H-2ax), 2.1 (d, J = 2Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.2-2.5 (m, 4H, NMe, H-5ax), 2.56-2.62 (m, 2H, H-3eq, H-5eq), 2.76 (d, J = 2Hz of d, J = 2Hz of d, J = 12Hz, 1H, H-6eq), 4.06 (q, J = 7.2Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.28 (d, J = 6Hz of d, J = 8Hz, 1H, pyridine H-5), 7.72 (d, J = 2Hz of d, J = 2Hz of d, J = 8Hz, 1H, pyridine H-4), 8.5 (d, J = 2Hz of d, J = 6Hz, 1H, pyridine H-6), 8.7 (d, J = 2Hz, 1H, pyridine H-2).
164k	H	H	H	Me	4-pyridyl	1729	0.76 (d, J = 7Hz, 3H, C-3 Me), 1.16 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.95 (d, J = 3Hz of d, J = 12Hz of d, J = 12Hz, 1H, H-6ax), 2.18-2.24 (m, 5H, H-5ax, NMe, H-2ax), 2.3 (d, J = 3Hz of d, J = 12Hz, 1H, H-2ax), 2.46 (d, J = 2Hz of d, J = 4Hz of d, J = 13Hz, 1H, H-5eq), 2.68 (d, J = 1Hz of d, J = 1Hz of d, J = 11Hz, 1H, H-2eq), 2.85 (m, 1H, H-3eq), 2.97 (br d, J = 12Hz, 1H, H-6eq), 4.04-4.22 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.26 (d, J = 1.7Hz of d, J = 5Hz,

							2H, pyridine H-3, H-5), 8.55 (d, J = 1.7Hz of d, J = 5Hz, 2H, pyridine H-2, H-6).
164l	H	H	Me	H	4-pyridyl	1729	1.08 (d, J = 7.3Hz, 3H, C-3-Me), 1.24 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.2-2.56 (m, 10H, H-3ax, H-5ax, H-5eq, NMe, H-2ax, H-2eq, H-6ax, H-6eq), 4.2 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.22 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.56 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).
164m	H	Me	H	H	4-pyridyl[c]	1729	1.18-1.2 (m, 6H, C-2 Me, $\mathrm{CH}\mathit{CH_3}$), 1.53 (d, J = 12Hz of d, J = 12Hz, 1H, H-3ax), 1.86-1.98 (m, 2H, H-5ax, H-6ax), 2.1 (m, 1H, H-2ax), 2.3 (s, 3H, NMe), 2.5-2.6 (m, 2H, H-3eq, H-5eq), 2.98 (m, 1H, H-6eq), 4.08 (d, J = 2Hz of q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 7.28 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.56 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).
164n	Me	H	H	H	4-pyridyl	1729	1.15 (m, 6H, C-2 Me, $\mathrm{CH_2}\mathit{CH_3}$), 1.91 (d, J = 12.6Hz of d, J = 12.6Hz, 1H, H-3ax), 1.95 (m, 1H, H-2ax), 2.04 (d, J = 2Hz

of d, J = 12.5Hz of d, J = 12.5Hz, 1H, H-6ax), 2.2 (s, 3H, NMe), 2.25 (d, J = 3Hz of d, J = 12.5Hz of d, J = 13Hz, 1H, H-5ax), 2.56 (m, 2H, H-3eq, H-5eq), 2.78 (d, J = 3Hz of d, J = 3Hz of d, J = 12.5Hz, 1H, H-6eq), 4.06 (q, J = 7Hz, 2H, $\mathit{CH}_2\ \mathrm{CH}_3$), 7.35 (d, J = 2Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.6 (d, 2Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).

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[a] **164e** and **164f** were a mixture in 11 : 8 ratio as calculated from integral values for the well separated ester methylene ($\mathit{CH}_2\mathrm{CH}_3$) shifts. The H-2ax, H-3eq, H-5ax, H-5eq and H-6eq proton shifts are not listed in the table because they were buried under the resonances of **164e** in the regions where they were expected. Comparison with the ^{1}H spectrum of **164j** on which ^{1}H homonuclear decoupling and heteronuclear shift correlated ^{1}H, ^{13}C two dimensional experiments were performed facilitated the assigments for compound **164e**.

[b] The spectrum was recorded for a mixture of **164i** and **164j** in a ratio of 5 : 1 calculated from the integrals for the well separated ester methylene ($\mathit{CH}_2\mathrm{CH}_3$) shifts.

[c] The spectrum was recorded for a mixture of **164m** and **164n** in a ratio of 7 : 1 calculated from the integrals for the well separated ester methylene ($\mathit{CH}_2\mathrm{CH}_3$) chemical shifts.

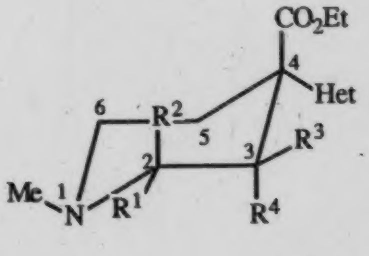
The unexpected C-2 methyl products (**164f, i, j, m , n**) exhibited ^{1}H and ^{13}C NMR chemical shifts for the C-2 methyl, H-2 and C-2 at lower fields compared to those of the 3-methyl isomers. The ^{13}C chemical shifts of these C-2 methyl products (**164f, i, j, m , n**) were similar to those of 1,2-dimethyl-4-piperidinol esters reported by Jones *et al.*[361] The C-2 methyl proton chemical shifts for the 2-methyl isomers were, **164f**, δ 1.22; **164i**, δ 1.18-1.24; **164j**, δ 1.15; **164m**, δ 1.18-1.2; **164n**, δ 1.15, are all at a lower field than those for the *cis*- (**164d**, **g** and **k**) and *trans*-(**164e**, **h** and **l**) 3-methyl stereoisomers, which appeared in the δ 0.7-0.8 and δ 1.06-1.1 ranges, respectively. The C-2 Me substituent of compounds **164f, i, j, m, n**, being on a carbon atom adjacent to the piperidine ring nitrogen, is deshielded by the electron withdrawing inductive effect (-I) of N-1 relative to the C-3 Me protons of compounds **164d, e, g, h, k, l**. The ^{13}C NMR chemical shifts for the C-2 Me substituents of compounds **164j** and **n** appeared at a lower field, δ 20.39 and δ 20.33, respectively, than the ^{13}C chemical shifts for the C-3 Me substituents of compounds **164g** and **h**, which appeared at δ 14.84 and δ 15.18, respectively.

The C-2 Me substituent present in compounds **164f, i, j, m, n** is equatorial as indicated by the fact that the H-3 chemical shifts for both the *cis*- (**164i, m**) and *trans*- (**164j, n**) stereoisomers exhibit only large geminal and large axial/axial couplings as follows: **164f**, J_{gem} = 12Hz, $J_{ax,ax}$ = 12Hz; **164i**, J_{gem} = 13Hz, $J_{ax,ax}$ = 11Hz; **164j**, J_{gem} = 12Hz, $J_{ax,ax}$ = 12Hz; **164m**, J_{gem} = 12Hz, $J_{ax,ax}$ = 12Hz; and **164n**, J_{gem} = 12.6Hz, $J_{ax,ax}$ = 12.6Hz, without any axial/equatorial coupling. This implies that the H-2 proton must be axial in both the *cis*- and *trans*- C-2 methyl-substituted stereoisomers (**164i, m**) and (**164f, j, n**) respectively. Casy and McErlane[362] have reported that the C-2 methyl substituent for both the *cis*- and *trans*-stereoisomers of 1,2-dimethyl-4-phenylpiperidinol esters related to compounds **158i, m** and **158j, n** respectively, was equatorial. These results indicate that the 4-(pyridyl) substituent of the *cis*- (2-Methyl/pyridyl) stereoisomers **158i, m** is equatorial, whereas the 4-(pyridyl) substituent of the *trans*-(2-methyl/pyridyl) stereoisomers **158j, n** is axial. The OCH$_2$*CH$_3$* methyl resonace for the *trans*-isomers **158j, n** (δ1.13) is at higher field than that of the *cis*-isomers **158i, m** (δ 1.18-1.24 range). This shielding is interpreted to mean that the aromatic ring of the *trans*-isomers (**158j, n**)is in the axial orientation (Fig. 13), so that the OCH$_2$*CH$_3$* is shielded as it passes above the plane of the aromatic ring during rotation about the C$_4$-CO$_2$Et bond.[362]

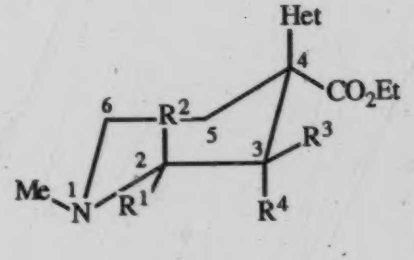
Heteronuclear shift correlated (^{1}H, ^{13}C) two dimensional NMR spectra for compounds **164g** and **j**, which are presented in Figs. 11 and 12, respectively, served to confirm their structural assigments.

A distinguishing feature in the ^{1}H NMR spectra for the *cis*-3-methyl diastereoisomers **164d, g, k** is that the resonance for the methylene group (*CH$_2$*CH$_3$) of the ethyl substituent appears as the AB component of a complex ABX$_3$ spin system. In the *trans*-3-methyl, *cis*-2-methyl and *trans*-2-methyl isomers, this methylene signal appears as a quartet. The difference may be due to a greater variation in chemical environments of the diastereotopic methylene protons when an axial C-3 methyl substituent is present in compounds **164** relative to an equatorial C-3 or C-2 methyl substituent. This is because it is only in these three compounds (**164d, g, k**) that the C-Me substituent adopts an axial orientation (Fig. 13).

Table 17: ^{13}C NMR Spectral Data for Compounds **164c**, **g**, **h**, **j** and **n**.


CO₂Et
4
Het
6
R²
5
3
R³
2
Me
1
N
R¹
R⁴

164c, g, h,


Het
4
CO₂Et
6
R²
5
3
R³
2
Me
1
N
R¹
R⁴

164j, n.

Entry.	R¹	R²	R³	R⁴	Het	^{13}C NMR ($CDCl_3$), δ
164c	H	H	H	H	4-pyridyl	13.83 ($CH_2\mathit{CH_3}$), 33.27 (C-3, C-5), 46.06 (NMe), 48.60 (C-4), 53.07 (C-2, C-6), 61.07 ($\mathit{CH_2}$ CH_3), 120.95 (pyridine C-3, C-5), 149.97 (pyridine C-2, C-6), 151.67 (pyridine C-4), 173.0 (C=O).
164g	H	H	H	Me	3-pyridyl	13.96 ($CH_2\mathit{CH_3}$), 14.84 (C-3 Me), 26.33 (C-5), 34.75 (C-3), 46.58 (NMe), 51.04 (C-4), 53.96 (C-6), 60.08(C-2), 61.07 ($\mathit{CH_2}CH_3$), 123.26 (pyridine C-5), 133.87 (pyridine C-4), 137.43 (pyridine C-3), 148.15 (pyridine C-6), 148.2 (pyridine C-2), 173.86 (C=O).

164h	H	H	Me	H	3-pyridyl	13.97 ($CH_2\mathit{CH_3}$), 15.18 (C-3 Me), 29.58 (C-5), 37.69 (C-3), 46.02 (NMe), 52.01 (C-4), 52.64 (C-6), 59.05 (C-2), 61.06 ($\mathit{CH_2}CH_3$), 123.14 (pyridine C-5), 134.47 (pyridine C-4), 137.52 (pyridine C-3), 147.93 (pyridine C-6), 148.86 (pyridine C-2), 173.37 (C=O).
164j	Me	H	H	H	3-pyridyl	13.9 ($CH_2\mathit{CH_3}$), 20.39 (C-2 Me), 32.25 (C-5), 40.23 (C-3), 42.64 (NMe), 52.22 (C-6), 54.17 (C-2), 61.14 ($\mathit{CH_2}CH_3$), 123.35 (pyridine C-5), 135.12 (pyridine C-3), 135.57 (pyridine C-4), 148.14 (pyridine C-6), 149.73 (pyridine C-2), 174.18 (C=O).
164n	Me	H	H	H	4-pyridyl	13.8 ($CH_2\mathit{CH_3}$), 20.3 (C-2 Me), 32.99 (C-5), 40.01 (C-3), 42.55 (NMe), 52.23 (C-6), 53.84 (C-4), 54.45 (C-2), 61.18 ($\mathit{CH_2}CH_3$), 122.98 (pyridine C-3, C-5), 148.88 (pyridine C-2, C-6), 173.96 (C=O).

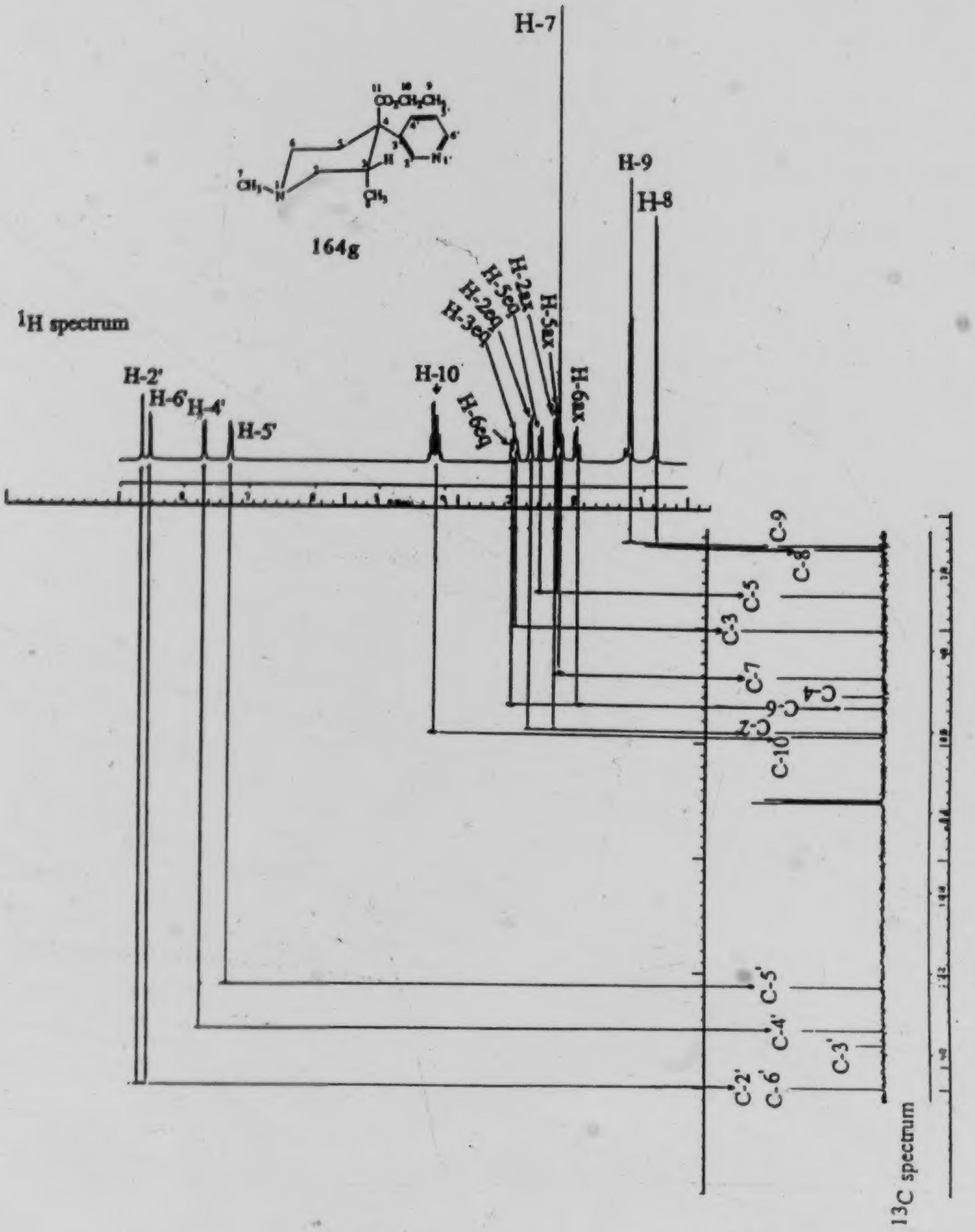


Fig. 11: Heteronuclear shift correlated (^1H, ^{13}C) two dimensional NMR spectrum for compound **164g**.

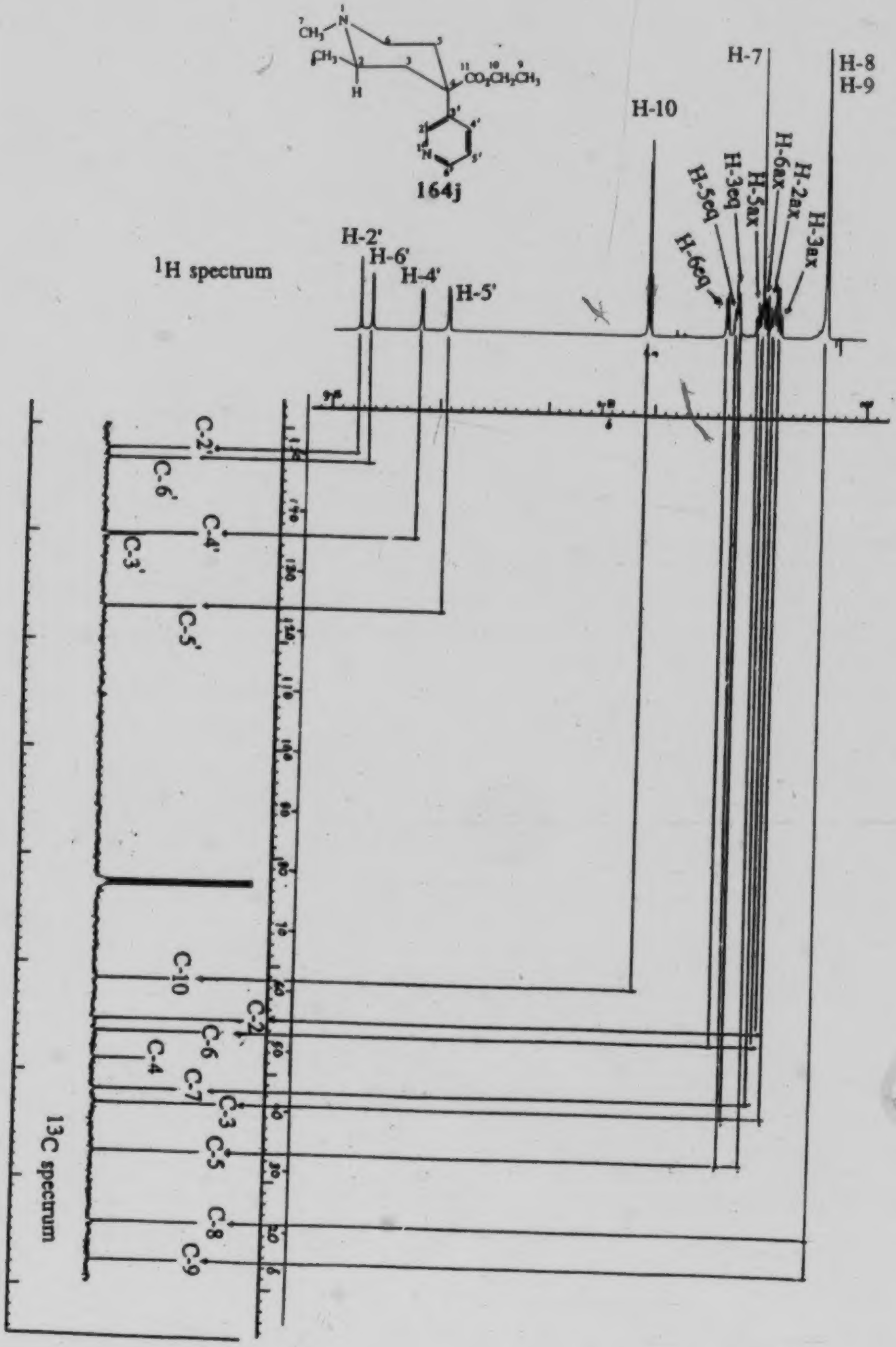
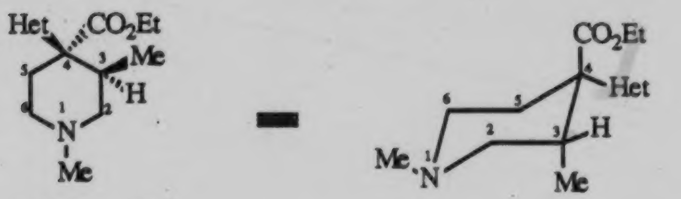
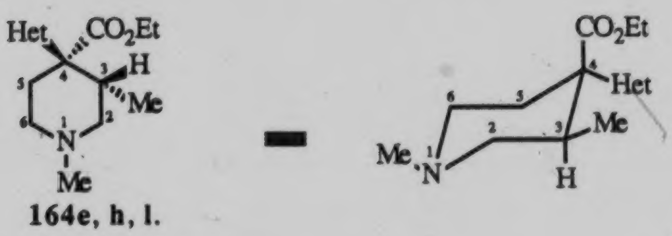


Fig. 12: Heteronuclear shift correlated (^{1}H, ^{13}C) two dimensional NMR spectrum for compound **164j**.


Het
CO2Et
Me
H
N
Me
1
2
3
4
5
6

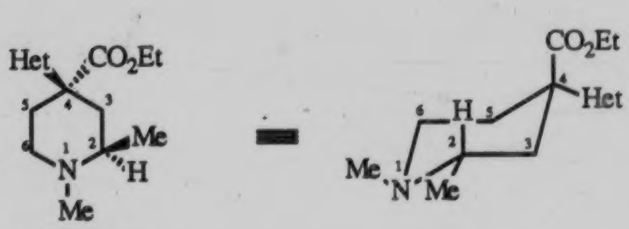
164d, g, k.

cis-3-methyl products


Het
CO2Et
H
Me
N
Me
1
2
3
4
5
6

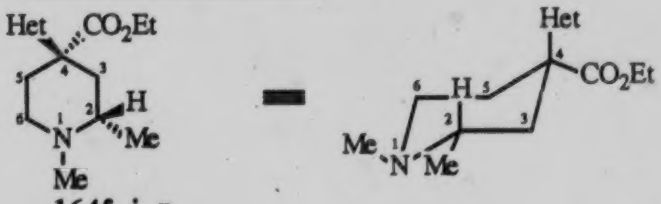
164e, h, l.

trans-3-methyl products


Het
CO2Et
Me
H
N
Me
1
2
3
4
5
6

164i, m.

cis-2-methyl products


Het
CO2Et
H
Me
N
Me
1
2
3
4
5
6

164f, j, n.

trans-2-methyl products

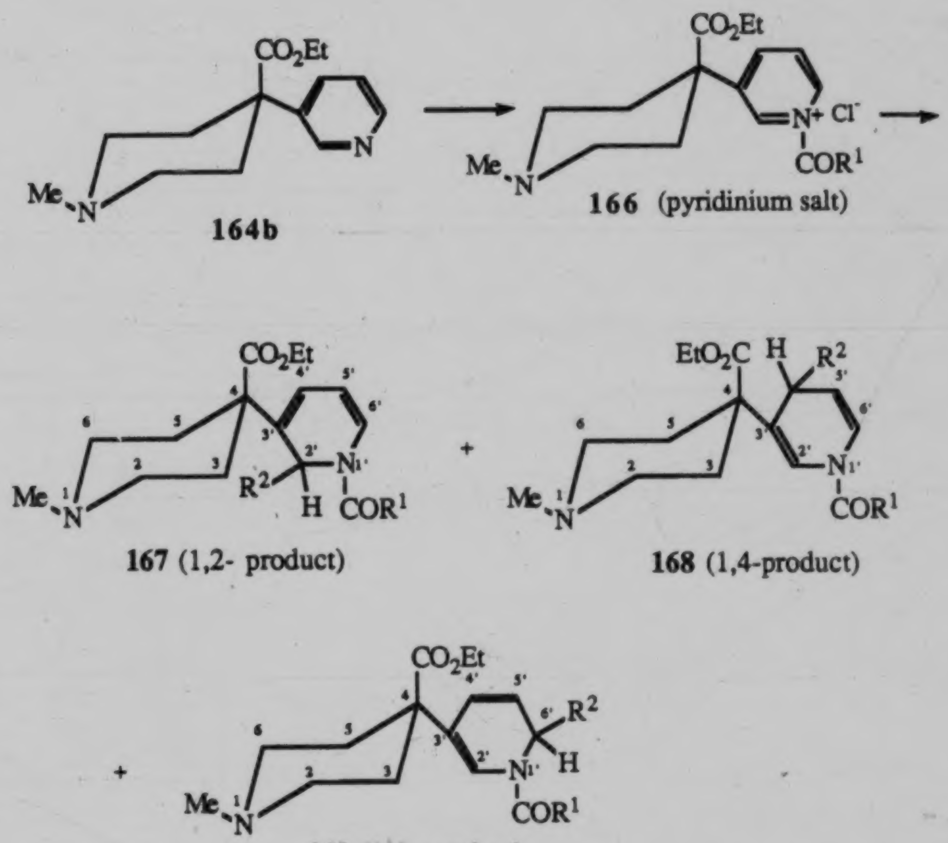
Fig. 13: Proposed solution conformations for 1,2- and 1,3-dimethyl-4-ethoxycarbonyl-4(pyridyl)piperidines (**164**).

The lower ratio of the *cis*- to *trans*-diastereoisomers which is in the 1 : 1.2-1 : 2

range for the 3-methyl compounds and 1 : 3.3.5-1 : 4.4 range for 2-methyl isomers (Table 15), indicates that there are more unfavorable nonbonding interactions in compounds **164** when the pyridyl ring and the C-methyl substituent are in *cis-* than when they are in the *trans-* relationship. This could explain, at least in part, why the reaction of **162b** with **163a** (Het = 2-pyridyl) did not produce the *cis*-(2-Me/pyridyl) diastereoisomer corresponding to **164i** and **164m**. The steric effect of the pyridine nitrogen lone-electron pair on the piperidine ring substituents is greatest for the 2-pyridyl ring relative to the 3- and 4-pyridyl rings.

3.2.6.1.0.0. Synthesis of 1-methyl-4-ethoxycarbonyl-4-(1-acyl-1,6(1,2)-dihydropyridyl)piperidines (169a-f and 171a-m)

The reaction of methylmagnesium chloride with the N-methoxycarbonylpyridinium chloride salt (**166**, R^1 = OMe) of **164b** in ether at -78 °C afforded a mixture of 1,2- , 1,4- and 1,6-dihydropyridines (**167a, 168a** and **169a**) in the ratio 3 : 1 : 7. A similar reaction using *n*-butylmagnesium chloride also afforded a mixture of 1,2-, 1,4- and 1,6-dihydropyridine products (**167b, 168b** and **169b**) in 76 % yield, in a ratio of 1 : 1.5 : 5. These mixtures could not be separated by TLC and therefore the ratios of products were calculated from intergrals of the dihydropyridine ring proton resonances in the ^{1}H NMR spectra of the mixtures run at 75 °C in DMSO-d_6 as solvent.



164b

166 (pyridinium salt)

167 (1,2- product)

168 (1,4-product)

169 (1,6- product)

The reaction using methylmagnesium chloride yielded the 1,2(1,6)-dihydropyridine products (**167a, 169a**) in a higher ratio (10 : 1) to the 1,4-isomer (**168a**) than the reaction employing *n*-butylmagnesium chloride, which gave a 1,2 (1,6)- to 1,4- ratio of 6 : 1.5. This is once again a reflection of the fact that a CH_3^- nucleophile is "harder" than a $CH_3(CH_2)_3^-$ nucleophile as previously discussed for the reactions of N-phenoxycarbonylpyridinium chloride salt of 1-methylpiperidylidene-2-(3-pyridine)sulfonamide (**150b**) with alkyl or phenylmagnesium chloride. The ratios of 1,2- to 1,6- dihydropyridine products afforded by the reactions with these two Grignard reagents (**167a** : **169a** = 3 : 7, **167b** : **169b** = 1 : 5), is a reflection of the difference in steric bulk of the methyl and *n*-butyl substituents. Reactions employing the less bulky methylmagnesium chloride afforded the 1,2-dihydropyridine product (**167**) in a higher ratio to the 1,6- isomer (**169**) relative to reactions in which the more bulky *n*-butylmagnesium chloride was used. In the pyridinium salt (**166**) the C-2' position is more sterically hindered than the C-6' position, the reason why 1,6-dihydropyridine products predominate over 1,2-dihydropyridine isomers.[348]

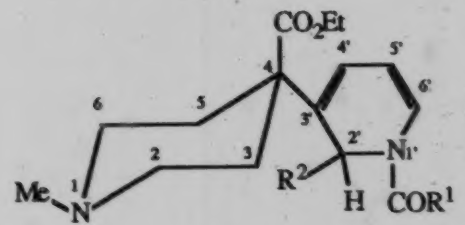
The addition reaction of phenylmagnesium chloride with N-methoxycarbonyl-, N-acetyl-, N-phenoxycarbonyl- and N-benzoylpyridinium salts of **164b** in THF at -78 °C, afforded the 1,6-dihydropyridine products **169c-f** as the sole products (51-81% chemical yields, Table 19).

Reactions of methyl or *n*-butylmagnesium chloride with N-phenoxycarbonyl, N-acetyl or N-benzoylpyridinium chloride salts of **164b** were not pursued because of the inability to separate the mixtures of 1,2-, 1,4- and 1,6-dihydropyridine products.

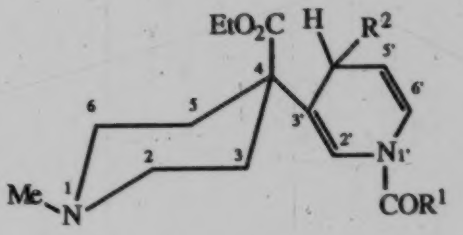
The ^{1}H NMR spectral data for compounds **167a**, **b**, **168a**, **b** and **169a**, **b** are summarized in Table 18.

Compound **171a** was obtained in 51% yield by sodium borohydride reduction of the N-phenoxycarbonylpyridinium chloride salt (**170**, R^1 = OPh) of **164c** in methanol at -78 °C.

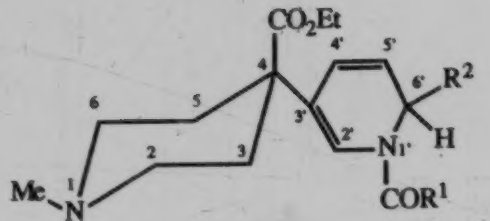
Table 18: IR and ^1H NMR Spectral Data for Compounds **167a-b**, **168a-b**, **169a-b**.



167



168

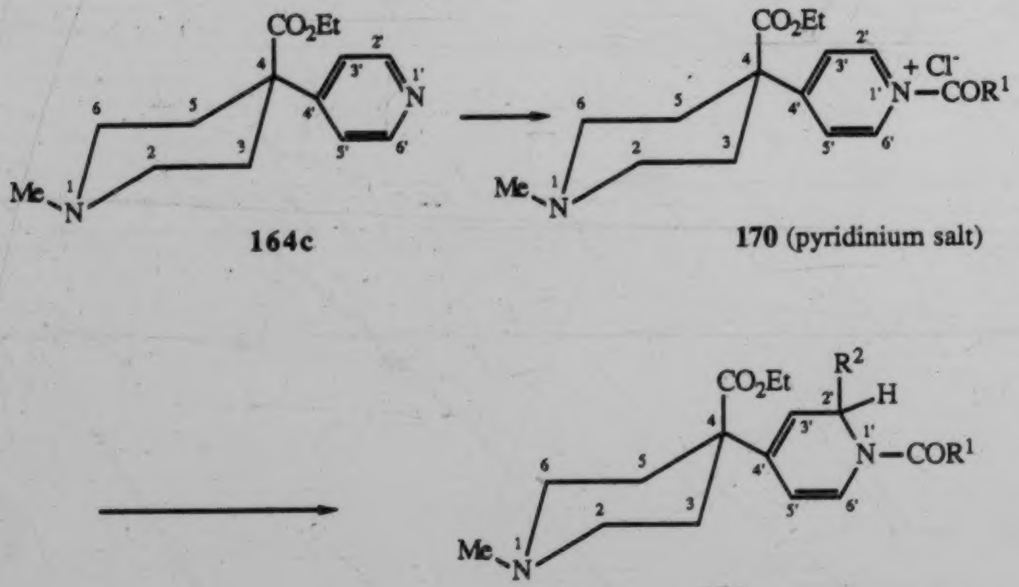


169

Entry	R^1	R^2	IR (C=O), cm^{-1}	^1H NMR (DMSO-d_6), 75 °C, δ,
167a	MeO	Me	1720	0.99 (d, J = 6Hz, 3H, C-2' Me), 1.15 (t, J = 6.5Hz, 3H, $CH_2\mathit{CH_3}$), 1.64 (m, 2h, H-3ax, H-5ax), 1.94 (m, 2H, H-2ax, H-6ax), 2.12-2.22 (m, 5H, NMe, H-3eq, H-5eq), 2.46 (m, 2H, H-2eq, H-6eq), 3.74 (s, 3H, OMe), 4.12 (m, 2H, $\mathit{CH_2}\,CH_3$), 4.92 (m, 1H, H-2'), 5.55 (d, J = 6Hz of d, J = 7Hz, 1H, H-5'), 5.76 (d, J = 7Hz, 1H, H-4'), 6.58 (s, 1H, H-2').
167b	MeO	*n*-Bu	1720	0.85 (t, J = 6Hz, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.12-1.35 (m, 8H, $CH_2\mathit{CH_3}$, $H\mathit{CHCH_2CH_2}\,CH_3$), 1.5 (m, 1H, $\mathit{HC}\,HCH_2CH_2\,CH_3$),

				1.6-1.8 (m, 2H, H-3ax, H-5ax), 1.96-2.24 (m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.52-2.68 (m, 2H, H-2eq, H-6eq), 3.75 (s, 3H, OMe), 4.14 (m, 2H, $\mathit{CH_2}\,\mathrm{CH_3}$), 5.1 (m, 1H, H-2'), 5.75 (d, J = 6Hz of d, J = 8Hz, 1H, H-5'), 5.95 (d, J = 8Hz, 1H, H-4'), 6.62 (d, J = 6Hz, 1H, H-6').
168a	OMe	Me	1720	0.95 (d, J = 6Hz, 3H, C-4' Me), 1.15 (t, J = 6.5Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.64 (m, 2h, H-3ax, H-5ax), 2.02-2.25(m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.46 (m, 2H, H-2eq, H-6eq), 3.8 (s, 3H, OMe), 4.12 (m, 2H, $\mathit{CH_2}\,\mathrm{CH_3}$), 5.14 (m, 1H, H-4'), 5.74 (d, J = 7Hz of d, J = 7Hz, 1H, H-5'), 6.75 (d, J = 7Hz, 1H, H-6'), 6.58 (s, 1H, H-2').
168b	OMe	*n*-Bu	1720	0.85 (t, J = 6Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.12-1.35 (m, 8H, $\mathrm{CH_2}\mathit{CH_3}$, $\mathrm{H}\mathit{CHCH_2CH_2}\,\mathrm{CH_3}$), 1.5 (m, 1H, $\mathit{HC}\,\mathrm{HCH_2CH_2\,CH_3}$), 1.6-1.8 (m, 2H, H-3ax, H-5ax), 1.96-2.24 (m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.52-2.68 (m, 2H, H-2eq, H-6eq), 3.78 (s, 3H, OMe), 4.14 (m, 2H, $\mathit{CH_2}\,\mathrm{CH_3}$), 4.88 (m, 1H, H-4'), 5.56 (d, J = 7Hz of d, J = 7Hz, 1H, H-5'), 6.78 (d, J = 7Hz, 1H, H-6'), 6.62 (s, 1H,

				H-6').
169a	OMe	Me	1720	1.04 (d, J = 6Hz, 3H, C-6' Me), 1.15 (t, J = 6.5Hz, 3H, $\mathrm{CH_2}CH_3$), 1.64 (m, 2h, H-3ax, H-5ax), 2.02 (m, 2H, H-2ax, H-6ax), 2.12-2.22 (m, 5H, NMe, H-3eq, H-5eq), 2.46 (m, 2H, H-2eq, H-6eq), 3.74 (s, 3H, OMe), 4.12 (m, 2H, CH_2 $\mathrm{CH_3}$), 4.7 (m, 1H, H-6'), 5.74 (d, J = 6Hz of d, J = 7Hz, 1H, H-5'), 5.98 (d, J = 7Hz, 1H, H-4'), 6.55 (s, 1H, H-2').
169b	OMe	*n*-Bu	1720	0.85 (t, J = 6Hz, 3H, $\mathrm{CH_2CH_2CH_2}CH_3$), 1.12-1.35 (m, 8H, $\mathrm{CH_2}CH_3$, $\mathrm{H}CHCH_2CH_2$ $\mathrm{CH_3}$), 1.5 (m, 1H, HC $\mathrm{HCH_2CH_2}$ $\mathrm{CH_3}$), 1.6-1.8 (m, 2H, H-3ax, H-5ax), 1.96-2.24 (m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.52-2.68 (m, 2H, H-2eq, H-6eq), 3.75 (s, 3H, OMe), 4.14 (m, 2H, CH_2 $\mathrm{CH_3}$), 4.65 (m, 1H, H-6'), 5.75(d, J = 6Hz of d, J = 8Hz, 1H, H-5'), 6.04 (d, J = 8Hz, 1H, H-4'), 6.6 (s, 1H, H-2').



164c

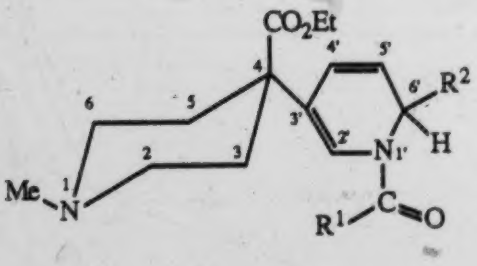
170 (pyridinium salt)

171

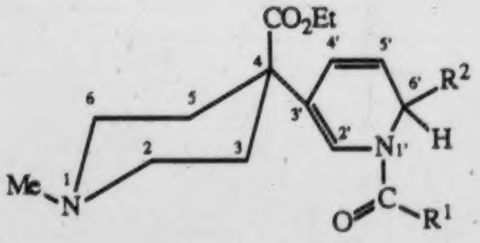
Addition of methyl, *n*-butyl or phenylmagnesium chloride to N-acylpyridinium salts (**170**) of **164c** in THF at -78 °C, afforded the 1,2-dihydropyridines **171b-m** as single products (51-73 % chemical yields, Table 19).

The IR and ^{1}H NMR data for compounds **169c-f** and **171a-m** which are summarized in Table 20 are consistent with the assigned structures. The piperidine ring has a similar solution conformation as in the parent pyridine compounds **164b, c.**

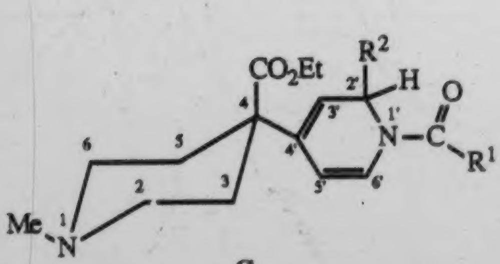
Compounds **167, 168, 169** and **171** exhibited rotational isomerism resulting from the presence of the amide or carbamate group as previously discussed (see section **3.2.4.1.1.0.**).The rotameric configurations for compounds **169** and **171** are represented by structures **E, F** and **G, H,** respectively.



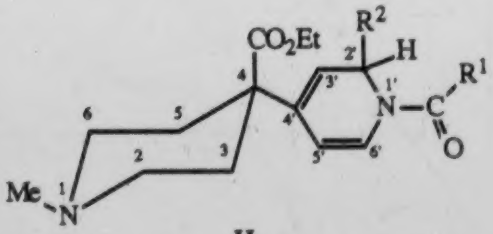
E



F



G



H

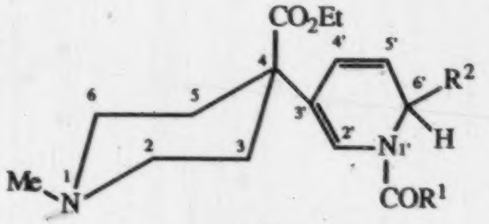
The ^{1}H NMR characteristics of the rotational isomers of compounds **163** and **164**, their rotameric ratios at 25 $^{\circ}$C and coalescence behaviour at higher temperatures are summarized in Table 21.

Rotational isomerism was more prevalent with the carbamates than with the amides. The reason for this difference is not apparent, but it implies that the presence of a N-1' methoxy (OMe) or phenoxy (OPh) substituent in **169c**, **171a-g** gives rise to a higher rotational energy barrier for the N-to-carbonyl bond, relative to a N-1' alkyl (Me) or phenyl (Ph) substituent present in compounds **171h-m**. The OMe and OPh substituents of compounds **171a-g** exhibit a higher electron-donating (+I) inductive effect relative to the corresponding Me and Ph substituents of compounds **164h-m.** Therefore the C-N bond π-electron density of the carbamates may be higher relative to the C-N bond of the amides. It has been reported that substituents that tend to decrease the C-N electron density tend to lower the barrier to rotation.[351]

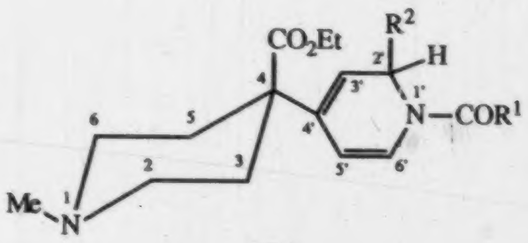
Similar to the observation for 1-methylpiperidylidene-2-(dihydropyridyl)sulfonamides (**150-152**), the protons that exhibited dual resonances were primarily those on the dihydropyridine rings of compounds **167-171**. The dual resonance data for compounds **169c** and **171f** presented in Table 21 show that the OMe group also exhibited dual resonance peaks.

The difference in chemical shifts between dual rotamer peaks decreased with increasing distance of the protons from N-1'. Thus for compound **169c** the H-2' dual resonance peaks exhibited the largest separation in chemical shifts (0.1 ppm), whereas the H-4' dual peaks showed the least separation (0.02 ppm). Rotamer peaks generally coalesced at temperatures between 60 and 75 ^{o}C

Table 19: Physical Data for 1-Methyl-4-ethoxycarbonyl-4-(dihydropyridinyl)piperidines (**169c**-**f** and **171a**-**m**).



169



171

Entry	R^1	R^2	Physical state	%Yield	Formula	Rf[a]	Microanalysis[b]: Calcd.(Found) C	H	N	Exact Mass: Calcd.(Found)
169c	OMe	Ph	oil	61	$C_{22}H_{28}N_2O_4$	0.75	44.14(44.05)	5.01(4.92)	4.68(4.66)	
169d	Me	Ph	oil	81	$C_{22}H_{28}N_2O_3$	0.53	45.29(45.29)	5.18(4.98)	4.88(4.72)	
169e	OPh	Ph	oil	76	$C_{27}H_{30}N_2O_4$	0.76	49.70(50.34)	4.79(5.04)	4.29(4.34)	
169f	Ph	Ph	oil	51	$C_{27}H_{30}N_2O_3$	0.84	51.03(51.02)	4.95(4.83)	4.41(4.54)	
171a	OPh	H	oil	51	$C_{21}H_{26}N_2O_4$	0.67	67.36(67.04)	7.53(7.12)	7.48(7.42)[c]	
171b	OPh	Me	oil	70	$C_{22}H_{28}N_2O_4$	0.68	44.16(43.81)	5.05(4.91)	4.68(4.55)	
171c	OPh	*n*-Bu	oil	66	$C_{25}H_{34}N_2O_4$	0.89	47.48(47.14)	5.58(5.51)	4.43(4.41)	
171d	OPh	Ph	oil	72	$C_{27}H_{30}N_2O_4$	0.80	48.37(48.20)	4.96(4.76)	4.18(4.32)	
171e	MeO	Me	oil	50	$C_{17}H_{26}N_2O_4$	0.71	38.72(39.24)	5.16(5.25)	5.31(5.42)	

171f	OMe	*n*-Bu	oil	73	$C_{20}H_{32}N_2O_4$	0.85	42.19(42.22)	5.84(5.75)	4.92(4.83)	
171g	OMe	Ph	oil	65	$C_{22}H_{28}N_2O_4$	0.78	44.14(44.00)	5.01(4.75)	4.68(4.27)	
171h	Ph	Me	oil	54	$C_{22}H_{28}N_2O_3$	0.76				368.2100(368.2090)
171i	Ph	*n*-Bu	oil	61	$C_{25}H_{34}N_2O_3$	0.88				410.2569(410.2567)
171j	Ph	Ph	oil	60	$C_{27}H_{30}N_2O_3$	0.80				430.2257(430.2251)
171k	Me	Me	oil	52	$C_{17}H_{26}N_2O_3$	0.56[d]	38.58(38.65)	5.29(5.71)	5.28(5.30)	
171l	Me	*n*-Bu	oil	60	$C_{20}H_{32}N_2O_3$	0.67[d]				348.2413(348.2409)
171m	Me	Ph	oil	55	$C_{22}H_{28}N_2O_3$	0.62[d]	44.61(44.82)	5.06(5.03)	4.73(4.65)	

---

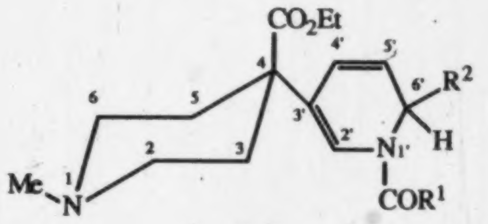
[a] Silica gel, MeOH : $CHCl_3$ (1 : 1 v/v) unless otherwise stated.

[b] Calculated for the hexachloroplatinic acid salts except for **171a**. Two molecules of the dihydropyridine (**169** or **171**) combined with one molecule of hexachloroplatinic acid ($H_2PtCl_6.xH_2O$).The following were the x values: for compounds **169d**, **e**, **f**, **171c**, **e** and **f** x = 0; for compounds **169c**, **171b** and **g** x = 1 and for compounds **171d**, **h** and **m** x = 2.

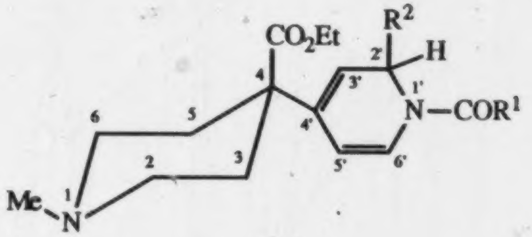
[c] Calculated for $C_{21}H_{26}N_2O_4.1/4\ H_2O$.

[d] Silica gel, MeOH : $CHCl_3$ (1 : 7 v/v).

Table 20: IR and ^{1}H NMR Spectral Data for Compounds **169c-f** and **171a-m**


CO2Et
Me
N
1
2
3
4
5
6
2'
3'
4'
5'
6'
N1'
R2
H
COR1

169


CO2Et
Me
N
1
2
3
4
5
6
1'
2'
3'
4'
5'
6'
R2
H
N—COR1

171

Entry	R^1	R^2	IR, cm^{-1}	^{1}H NMR, $\delta^{a,b}$
169c	OMe	Ph	1721 (C=O), 1650 (C=C).	DMSO-d_6, 75 ^{o}C: 1.05 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.7 (m, 2H, H-3ax, H-5ax), 2.06 (m, 2H, H-2ax, H-6ax), 2.18 (m, 5H, H-3eq, H-5eq, NMe), 2.56 (m, H-2eq, H-6eq), 3.75 (s, 3H, OMe), 4.14 (q, J = 7Hz, 2H, $\mathit{CH_2}CH_3$), 5.78 (d, J = 6Hz, 1H, H-6'), 5.9 (d, J = 6Hz of d, J = 8.5Hz, 1H, H-5), 6.14 (d, J = 8.5Hz, 1H, H-4'), 6.75 (s, 1H, H-2'), 7.34 (m, 5H, phenyl hydrogens). Complete coalescence of dual rotameric peaks occurred.
				DMSO-d_6, 25 ^{o}C: 1.15 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.65 (m, 2H, H-3ax, H-5ax), 2.0 (m, 2H, H-2ax, H-6ax), 2.12- 2.2 (m, 5H, NMe, H-3eq, H-5eq), 2.58 (m, 2H, H-2eq, H-6eq), 3.76[3.7] (s, 3H, OMe), 4.12(q, J = 7Hz, 2H, $\mathit{CH_2}CH_3$), 5.8[5.74] (d, J = 7.7Hz, 1H, H-4'), 6.68[6.78]

				(s, 1H, H-2'), 7.3-7.38 (m, 5H, phenyl hydrogens).
169d	Me	Ph	1725 (C=O), 1650 (C=C).	25 °C: 1.25 (t, J = 6.5Hz, 3H, CH_2CH_3), 1.73 (m, 2H, H-3ax, H-5ax), 1.9-2.3 (m, 10H, H-2ax, H-6ax, C(O)Me, NMe, H-3eq, H-5eq), 2.7 (m, 2H, H-2eq, H-6eq), 4.2 (q, J = 6.5Hz, 2H, CH_2CH_3), 5.84 (d, J = 6Hz of d, J = 8Hz,1H, H-5'), 6.2-6.3 (m, 2H, H-4', H-6'), 6.43 (s, 1H, H-2'), 7.3 (m, 5H, phenyl hydrogens); major rotamer.
169e	OPh	Ph	1725 (C=O), 1650 (C=C).	60 °C: 1.25 (t, J = 7Hz, 3H, CH_2CH_3), 1.87.(m, 2H, H-3ax, H-5ax), 2.2 (m, 2H, H-2ax, H-6ax), 2.28 (s, 3H, NMe), 2.38 (m, 2H, H-3eq, H-5eq), 2.74 (m, 2H, H-2eq, H-6eq), 4.2 (q, J = 7Hz, 2H, CH_2CH_3), 5.8 (d, J = 6Hz of d, J = 8.5Hz, 1H, H-5'), 5.92 (d, J = 6Hz, 1H, H-6'), 6.22 (d, J = 8.5Hz, 1H, H-4'), 6.92 (s, 1H, H-2'), 7.15 (m, 2H, *o*-phenoxy hydrogens), 7.2 (t, J = 8Hz, 1H, *p*-phenoxy hydrogen), 7.3 (m, 5H, phenyl hydrogens), 7.45 (m, 2H, *m*-phenoxy hydrogens).
169f	Ph	Ph	1725 (C=O), 1660 (C=C).	25 °C: 1.25 (t, J = 7.5Hz, 3H, CH_2CH_3), 1.7 (m, 2H, H-3ax, H-5ax), 2.1(m, 2H, H-2ax, H-6ax), 2.2-2.32 (m, 5H, H-3eq, H-5eq, NMe), 2.7 (m, 2H, H-2eq, H-6eq), 4.16 (m, 2H, CH_2CH_3), 5.86 (m, 1H, H-5'), 6.24-6.36 (m, 3H, H-2', H-4', H-6'), 7.3-7.48 (m, 10H, phenyl hydrogens).

				58 °C: 1.22 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.7 (m, 2H, H-3ax, H-5ax), 2.11 (m, 2H, H-2ax, H-6ax) , 2.24 (m, 5H, NMe, H-3eq, H-5eq), 2.63 (m, 2H, H-2eq, H-6eq), 4.13 (m, 2H, $\mathit{CH_2}CH_3$), 5.94 (d, J = 6Hz of d, J = 8Hz, 1H, H-5'), 6.2 (br, 1H, H-6'), 6.28 (d, J = 7Hz, 1H, H-4'), 6.4 (br, 1H, H-2'), 7.28-7.45 (m, 10H, phenyl hydrogens).
				60 °C: 1.22 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.72 (m, 2H, H-3ax, H-5ax), 2.14 (m, 2H, H-2ax, H-6ax), 2.24 (m, 5H, NMe, H-3eq, H-5eq), 2.62 (m, 2H, H-2eq, H-6eq), 4.16 (m, 2H, $\mathit{CH_2}CH_3$), 5.97 (d, J = 6Hz of d, J = 8Hz, 1H, H-5'), 6.2 (br, 1H, H-6'), 6.28 (d, J = 8Hz, 1H, H-4'), 6.45 (br, 1H, H-2'), 7.3-7.48 (m, 10H, phenyl hydrogens).
171a	OPh	H	1721 (C=O), 1655 (C=C).	25 °C: 1.25 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.72 (m, 2H, H-3ax, H-5ax), 2.06 (m, 2H, H-2ax, H-6ax), 2.27 (s, 3H, NMe), 2.29 (m, 2H, H-3eq, H-5eq), 2.76 (m, 2H, H-2eq, H-6eq), 4.18 (q, J = 7Hz, 2H, $\mathit{CH_2}CH_3$), 4.43 [4.56] (d, J = 3.7Hz, 2H, H-2'), 5.32[5.34] (d, J = 1.8Hz, of d, J = 8.3Hz, 1H, H-5'), 5.42 (m, 1H, H-3'), 6.85[6.8](d, J = 8.3Hz, 1H, H-6'), 7.11(d, J = 7.4Hz, 2H, *o*-phenyl hydrogens), 7.2 (t, J = 7.4Hz, 1H, *p*-phenyl hydrogen), 7.39 (t, J = 7.4Hz, 2H, *m*-phenyl hydrogens).

				58 °C: 1.25 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.75 (d, J = 3.5 of d, J = 11.7Hz of d, J = 11.7Hz, 2H, H-3ax, H-5ax), 2.09 (t, J = 2.5Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.26 (m, 5H, H-3eq, H-5eq, NMe), 2.74 (d, J = 2.5Hz of d, J = 2.5Hz of d, J = 14.4Hz, 2H, H-2eq, H-6eq), 4.18 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 4.46[4.48] (br, 2H, H-2'), 5.34 (d, J = 7Hz, 1H, H-5'), 5.44 (m, 1H, H-3'), 6.84 (d, J = 7Hz, 1H, H-6'), 7.14 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.2 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.35 (t, J = 8Hz, 2H, *m*-phenyl hydrogens).
171b	OPh	Me	1721 (C=O), 1640 (C=C).	25 °C: 1.17 (d, J = 6.5Hz, 3H, C-2' Me), 1.26 (t, J = 6Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.18 (m, 2H, H-3ax, H-5ax), 2.35-2.42 (m, 7H, NMe, H-2ax, H-6ax, H-3eq, H-5eq), 3.08 (m, 2H, H-2eq, H-6eq), 4.22 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 4.94[5.02] (m, 1H, H-2'), 5.36[5.38] (d, J = 7.8Hz, 1H, H-5'), 5.49 (d, J = 5.3Hz, 1H, H-3'), 6.84[6.79] (d, J = 7.8Hz, 1H, H-6'), 7.14 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.24 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.39 (t, J = 8Hz, 2H, *m*-phenyl hydrogens). 60 °C: 1.22 (d, J = 6Hz, 3H, C-2' Me), 1.3 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.4 (m, 2H, H-2ax, H-6ax), 2.54 (m, 5H, H-3eq, H-5eq, NMe), 3.1 (m, 2H, H-2eq, H-6eq), 4.24 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 5.2 (m, 1H, H-2'), 5.37 (d, J = 8Hz, 1H, H-5'), 5.5 (d, J = 6Hz, 1H, H-3'), 6.82

				(d, J = 8Hz, 1H, H-6'), 7.2 (d, J = 2Hz of d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.22 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.4 (t, J = 8Hz, 2H, *m*-phenyl hydrogens).
171c	OPh	*n*-Bu	1721 (C=O), 1640 (C=C).	25 °C: 0.86 (m, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.24 (t, J = 6Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.28-1.34 (m, 4H, $\mathrm{CH_2}\mathit{CH_2CH_2}\mathrm{CH_3}$), 1.54 (m, 1H, $\mathit{CH}\mathrm{H\ CH_2CH_2CH_3}$), 1.6 (m, 1H, $\mathit{CH}\ \mathrm{HCH_2CH_2CH_3}$), 1.8 (m, 2H, H-3ax, H-5ax), 2.12 (m, 2H, H-2ax, H-6ax), 2.3 (s, 3H, NMe), 2.35 (m, 2H, H-3eq, H-5eq), 2.8 (m, 2H, H-2eq, H-6eq), 4.18 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 4.84[4.92] (m, 1H, H-2'), 5.39 [5.46] (d, J = 2Hz of d, J = 8.5Hz, 1H, H-5'), 5.52 (d, J = 6.2Hz, 1H, H-3'), 6.85[6.8] (d, J = 8.5Hz, 1H, H-6'), 7.14 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.25(t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.28 (m, 2H, *m*-phenyl hydrogens). 60 °C: 0.88 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.25 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.3 (m, 4H, $\mathrm{CH_2}\mathit{CH_2CH_2}\mathrm{CH_3}$), 1.54-1.7 (m, 2H, $\mathit{CH_2}\mathrm{CH_2CH_2CH_3}$), 1.84 (m, 2H, H-3ax, H-5ax), 2.18 (m, 2H, H-2ax, H-6ax), 2.28-2.34 (m, 5H, NMe, H-3eq, H-5eq), 2.78 (m, 2H, H-2eq, H-6eq), 4.2 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 4.9 (br, 1H, H-2'), 5.44 (br, 1H, H-5'), 5.53(d, J = 6Hz, 1H, H-3'), 6.84 (d, J = 8Hz, 1H, H-6'), 7.16 (d, J = 8Hz, *o*-phenyl hydrogens), 7.25 (t, J = 8Hz, 1H, *p*-phenyl hydrogens), 7.38 (t, J = 8Hz, 2H, *m*-phenyl hydrogens).

171d	OPh	Ph	1729 (C=O), 1640 (C=C).	25 °C: 1.26 (m, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.8 (m, 2H, H-3ax, H-5ax), 2.12 (m, 2H, H-2ax, H-6ax), 2.18 (s, 3H, NMe), 2.35 (m, 2H, H-3eq, H-5eq), 2.76 (m, 2H, H-2eq, H-6eq), 4.22 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 5.48[5.5] (d, J = 8Hz, 1H, H-5'), 5.6[5.64] (d, J = 6Hz, 1H, 1H, H-3'), 5.98 (d, J = 6Hz, 1H, H-2', 6.9[6.94] (d, J = 8Hz, 1H, H-6'), 7.14 (d, J = 8.5Hz, 2H, *o*-phenyl hydrogen), 7.25 (t, J = 8.5Hz, 1H, *p*-phenyl hydrogen), 7.3-7.45 (m, 7H, phenyl hydrogens). 60 °C: 1.26 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.8 (m, 2H, H-3ax, H-5ax), 2.14 (m, 2H, H-2ax, H-6ax), 2.24 (s, 3H, NMe), 2.34 (m, 2H, H-3eq, H-5eq), 2.72 (m, 2H, H-2eq, H-6eq), 4.2 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 5.48 (d, J = 2Hz of d, J = 8Hz, 1H, H-5'), 5.64 (d, J = 6Hz, 1H, H-3'), 5.99 (d, J = 6Hz, 1H, H-2'), 6.93 (d, J = 8Hz, 1H, H-6'), 7.05-7.46 (m, 10H, phenyl hydrogens).
171e	OMe	Me	1721 (C=O), 1650 (C=C).	25 °C: 1.1(d, J = 6Hz, 3H, C-2' Me), 1.25 (t, J = 6Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.28 (m, 2H, H-3ax, H-5ax), 2.44 (m, 2H, H-2ax, H-6ax), 2.68-2.84 (m, 5H, NMe, H-3eq, H-5eq), 3.35 (m, 2H, H-2eq, H-6eq), 3.8 (s, 3H, OMe), 4.2(m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 4.87[4.78] (br, 1H, H-2'), 5.22[5.28](br, 1H, H-5'), 5.43 (br, 1H, H-3'), 6.64[6.75] (d, J = 8Hz, 1H, H-6') 60 °C: 1.11 (d, J = 6Hz, 3H, C-2'Me), 1.26 (t, J = 6Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 2.26 (m, 2H, H-3ax, H-5ax), 2.39 (m, 2H, H-2ax, H-6ax), 2.6 (s, 3H, NMe), 2.68(m, 2H, H-3eq, H-5eq),

				3.2 (m, 2H, 2H, H-2eq, H-6eq), 3.8 (s, 3H, OMe), 4.2 (m, 2H; $\mathit{CH_2}$ CH_3), 4.8 (m, 1H, H-2'), 5.24 (d, J = 2Hz of d, J = Hz, 1H, H-5'), 5.42 (d, J = 6Hz, 1H, H-3'), 6.7 (d, J = 8Hz, 1H, H-6').
171f	OMe	*n*-Bu	1720 (C=O), 1630 (C=C).	25 °C: 0.9 (m, 3H, $CH_2CH_2CH_2\mathit{CH_3}$), 1.16-1.43 (m, 8H, $CH_2\mathit{CH_3}$, $\mathit{CH}HC\mathit{H_2}\mathit{CH_2}CH_3$), 1.59-1.7 (m, 1H, $\mathit{CH}HCH_2CH_2CH_3$), 2.23 (m, 2H, H-3ax, H-5ax), 2.53 (m, 2H, H-2ax, H-6ax), 2.63-2.78 (m, 5H, NMe, H-3eq, H-5eq), 3.3 (m, 2H, H-2eq, H-6eq), 3.81[3.77] (s, 3H, OMe), 4.2 (m, 2H, $\mathit{CH_2}CH_3$), 4.83[4.68] (m, 1H, H-2'), 5.24[5.3] (d, J = 8Hz, 1H, H-5'), 5.45 (br, 1H, H-3'), 6.7[6.83] (d, J = 8Hz, 1H, H-6'). 60 °C: 0.9 (t, J = 7.5Hz, 3Hz, $CH_2CH_2CH_2\mathit{CH_3}$), 1.24-1.32 (m, 7H, $CH_2\mathit{CH_3}$, $CH_2\mathit{CH_2}\mathit{CH_2}CH_3$), 1.46 (m, 1H, CH $HCH_2CH_2CH_3$), 1.62 (m, 1H, C $\mathit{H}HCH_2CH_2CH_3$), 2.28 (m, 2H, H-3ax, H-5ax), 2.42 (m, 2H, H-2ax, H-6ax), 2.6-2.7 (m, 5H, NMe, H-3eq, H-5eq), 3.2 (m, 2H, H-2eq, H-6eq), 3.84 (s, 3H, OMe), 4.23 (m, 2H, $\mathit{CH_2}CH_3$), 4.8 (br, 1H, H-2'), 5.28 (d, J = 9Hz, 1H, H-5'), 5.49 (d, J = 6.2Hz, 1H, H-3'), 6.76 (br, 2H, H-6').
171g	OMe	Ph	1721 (C=O), 1650 (C=C).	25 °C: 1.14 (m, 3H, $CH_2\mathit{CH_3}$), 1.85 (m, 2H, H-3ax, H-5ax), 2.2 (m, 2H, H-2ax, H-6ax), 2.32 (m, 5H, NMe, H-3eq, H-5eq), 2.82 (m, 2H, H-2eq, H-6eq), 3.76 (s, 3H, OMe), 4.1-4.25

(m, 2H, CH_2CH_3), 5.32[5.38] (d, J = 8.5Hz, 1H, H-5'), 5.55 (m, 1H, H-3'), 5.92[5.76] (d, J = 6.2Hz, 1H, H-2'), 6.7[6.9] (d, J = 8.5Hz, 1H, H-6'), 7.3 (m, 4H, *o*- and *m*-phenyl hydrogens), 7.4 (m, 1H, *p*-phenyl hydrogen).

60 °C: 1.2 (t, J = 7.5Hz, 3H, CH_2CH_3), 1.9 (m, 2H, H-3ax, H-5ax), 2.2-2.3 (m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.78 (m, 2H, H-2eq, H-6eq), 3.75 (s, 3H, OMe), 4.16 (m, 2H, CH_2CH_3), 5.28 (d, J = 2Hz of d, J = 8Hz, 1H, H-5'), 5.5 (d, J = 6Hz, 1H, H-3'), 5.8 (br, 1H, H-2'), 6.72 (br, 1H, H-6'), 7.25 (m, 3H, *o*- and *p*-phenyl hydrogens), 7.36 (m, 2H, *m*-phenyl hydrogens).

171h	Ph	Me	1730 (C=O), 1645 (C=C).	25 °C: 1.2 (d, J = 6Hz, 3H, C-2' Me), 1.26 (t, J = 7Hz, 3H, CH_2CH_3), 1.76 (m, 2H, H-3ax, H-5ax), 2.08 (m, 2H, H-2ax, H-6ax), 2.27 (s, 3H, NMe), 2.32 (m, 2H, H-3eq, H-5eq), 2.74 (m, 2H, H-2eq, H-6eq), 4.22 (m, 2H, CH_2CH_3), 5.26 (m, 1H, H-2'), 5.34 (d, J = 8.5Hz, 1H, H-5'), 5.6 (d, J = 6Hz, 1H, H-3'), 6.3 (d, J = 8.5Hz, 1H, H-6'), 7.44-7.54 (m, 5H, phenyl hydrogens).
				60 °C: 1.19 (d, J = 6Hz, 3H, C-2' Me), 1.26 (t, J = 6Hz, 3H, CH_2CH_3), 1.79 (d, J = 3Hz of d, J = 3Hz of d, J = 12Hz of d, J = 14Hz, 2H, H-3ax, H-5ax), 2.11(d, J = 2Hz of d, J = 2Hz of d,

				J = 12Hz, 2H, H-2ax, H-6ax), 2.26 (s, 3H, NMe), 2.3 (m, 2H, H-3eq, H-5eq), 2.7 (m, 2H, H-2eq, H-6eq), 4.2 (q, J = 7Hz, 2H, $CH_2\mathrm{CH_3}$), 5.19 (m, 1H, H-2'), 5.35 (d, J = 8Hz, 1H, H-5'), 5.58 (d, J = 6Hz, 1H, H-3'), 6.38 (d, J = 8Hz, 1H, H-6'), 7.4-7.54 (m, 5H, phenyl hydrogens).
171i	Ph	*n*-Bu	1729 (C=O), 1647 (C=C).	25 °C: 0.9 (t, J = 6Hz, 3H, $\mathrm{CH_2CH_2CH_2}CH_3$), 1.28 (t, J = 7.5Hz, 3H, $\mathrm{CH_2}CH_3$), 1.34 (m, 4H, $\mathrm{CH_2}CH_2CH_2\mathrm{CH_3}$), 1.54 (m, 1H, $CH\mathrm{HCH_2CH_2CH_3}$), 1.69-1.82 (m, 3H, $C\,H\mathrm{HCH_2CH_2CH_3}$, H-3ax, H-5ax), 2.1(m, 2H, H-2ax, H-6ax), 2.28 (s, 3H, NMe), 2.34 (m, 2H, H-3eq, H-5eq), 2.76 (m, 2H, H-2eq, H-6eq), 4.25.(q, J = 7.5Hz, 2H, $CH_2\mathrm{CH_3}$), 5.2 (m, 1H, H-2'), 5.33 (d, J = 8Hz, 1H, H-5'), 5.65 (d, J = 6.1Hz, 1H, H-3'), 6.34 (d, J = 8Hz, 1H, H-6'), 7.42-7.5 (m, 5H, phenyl hydrogens).
171j	Ph	Ph	1729 (C=O), 1637 (C=C).	60 °C: 1.26 (t, J = 7Hz, 3H, $\mathrm{CH_2}CH_3$), 1.8 (m, 2H, H-3ax, H-5ax), 2.11 (m, 2H, H-2ax, H-6ax), 2.28 (s, 3H, NMe), 2.37 (m, 2H, H-3eq, H-5eq), 2.78 (m, 2H, H-2eq, H-6eq), 4.22 (m, 2H, $CH_2\mathrm{CH_3}$), 5.4 (d, J = 8Hz, 1H, H-5'), 5.78 (d, J = 6Hz, 1H, H-3'), 6.28 (d, J = 6Hz, 1H, H-2') 6.44 (d, J = 8Hz, 1H, H-6'), 7.34-7.45 (m, 5H, *m*- and *p*-phenyl hydrogens, *m*-benzoyl hydrogens), 7.54 (m, 1H, *p*-benzoyl hydrogen), 7.58 (m, 2H, *o*-phenyl hydrogens), 7.84 (d, J =8.5Hz, 2H, *o*-benzoyl hydrogens).

				25 °C: 1.22 (t, J = 7Hz, $\mathrm{CH_2}\mathit{CH_3}$), 1.82 (m, 2H, H-3ax, H-5ax), 2.12 (m, 2H, H-2ax, H-6ax), 2.26 (s, 3H, NMe), 2.3 (m, 2H, H-3eq, H-5eq), 2.7 (m, 2H, H-2eq, H-6eq), 4.2 (m, 2H, $\mathit{CH_2}\,\mathrm{CH_3}$), 5.41 (d, J = 6Hz, 1H, H-5'), 6.33-6.42 (m, 2H, H-2', H-6'), 7.3 (m, 2H, phenyl hydrogens), 7.42-7.5 (m, 5H, *p*- and *m*-phenyl hydrogens, *m*-benzoyl hydrogens), 7.56 (m, 1H, *p*-benzoyl hydrogen), 7.84 (m, 2H, *o*-benzoyl hydrogens).
171k	Me	Me	1720 (C=O), 1650 (C=C).	25 °C: 1.05 (d, J = 6Hz, 3H, C-2' Me), 1.22 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.9 (m, 2H, H-3ax, H-5ax), 2.04 - 2.53 (m, 10H, C(O)Me, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 3.96 (m, 2H, H-2eq, H-6eq),4.2 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 5.26 (m, 1H, H-2'), 5.36 (d, J = 1.7Hz of d, J = 8.5Hz, 1H, H-5'), 5.4 (d, J = 5.9Hz, 1H, H-3'), 6.44 (d, J = 8.5Hz, 1H, H-6').
171l	Me	*n*-Bu	1720 (C=O), 1645 (C=C).	58 °C: 0.86 (t, J = 6.5Hz, 3H, $\mathrm{CH_2CH_2CH_2}\mathit{CH_3}$), 1.22-1.32 (m, 7H, $\mathrm{CH_2}\mathit{CH_3}$, $\mathrm{CH_2}\mathit{CH_2CH_2}\mathrm{CH_3}$), 1.44 (m, 1H, $\mathit{CH}\mathrm{HCH_2CH_2CH_3}$), 1.46 (m, 1H, $\mathrm{C}\,\mathit{H}\mathrm{HCH_2CH_2CH_3}$), 2.0 (m, 2H, H-3ax, H-5ax), 2.16 (s, 3H, C(O)Me), 2.3-2.42 (m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 2.92 (m, 2H, 2H, H-2eq, H-6eq), 4.2 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 5.14 (m, 1H, H-2'), 5.38 (d, J = 8.5Hz, 1H, H-5'), 5.56 (d, J = 6Hz, 1H,H-3'), 6.5 (d, J = 8.5Hz, 1H, H-6').

171m	Me	Ph	1730 (C=O), 1660 (C=C).	60 °C: 1.25 (m, 3H, $CH_2\mathit{CH_3}$), 2.17 (s, 3H, C(O)Me), 2.43 (m, 2H, H-3ax, H-5ax), 2.65-2.87(m, 7H, H-2ax, H-6ax, NMe, H-3eq, H-5eq), 3.28 (m, 2H, H-2eq, H-6eq),. 4.22 (m, 2H, $\mathit{CH_2}CH_3$), 5.4 (d, J = 8.5Hz, 1H, H-5'), 5.66 (d, J = 6Hz, 1H, H-3'), 6.26(m, 1H, H-2'), 6.58 (m, 1H, H-6'), 7.3 (m, 5H, phenyl hydrogens).

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[a] $CDCl_3$ was used as solvent unless otherwise stated.

[b] Chemical shift value in square brackets is that for the corresponding resonance in the minor rotameric product.

Table 21: ^{1}H NMR Dual Resonance and Temperature Effect Data for Some Rotamers of Compounds163 and 164.

Compd.	Solvent	Dual Resonance	Shift at 25 °C, δ		Rotameric ratio at 25 °C	Coalescence	
		Peaks	Major	Minor	(Reference peak)	Shift (δ)	Temp. °C
169c	DMSO-d_6/$CDCl_3$	OMe	3.74	3.70	8:5 (OMe)	3.75	75
		H-6'	5.80	5.74		5.78	75
		H-4'	6.16	6.12		6.14	75
		H-2'	6.66	6.68		6.75	75
171a	$CDCl_3$	H-2'[a]	4.43	4.56	5:3 (H-2')		
		H-5'	5.32	5.34		5.34	58
		H-6'	6.85	6.80		6.86[b]	58
171b	$CDCl_3$	H-2'	4.94	5.02	2:1 (H-2')	5.02	60
		H-5'	5.36	5.38		5.40	60
		H-6'	6.84	6.79		6.85	60
171c	$CDCl_3$	H-2'	4.84	4.92	3:2 (H-2')	4.90[b]	60
		H-5'	5.39	5.46		5.44[b]	60
		H-6'	6.85	6.80		6.84[b]	60
171d	$CDCl_3$	H-5'	5.48	5.50		5.48	60

		H-3'	5.60	5.64	1:1 (H-6')	5.64	60
		H-6'	6.90	6.94		6.93	60
171e	$CDCl_3$	H-2'	4.87	4.78		4.80	60
		H-5'	5.22	5.28	3:2 (H-2')	5.24	60
		H-6'	6.64	6.75		6.70	60
171f	$CDCl_3$	OMe	3.81	3.77		3.84	60
		H-2'	4.83	4.68		4.80[b]	60
		H-5'	5.24	5.30	2:1 (H-6')	5.28	60
		H-6'	6.70	6.83		6.76[b]	60
171g	$CDCl_3$	H-5'	5.32	5.38		5.28	60
		H-2'	5.92	5.76	3:2 (H-6')	5.80[b]	60
		H-6'	6.70	6.90		6.72[b]	60

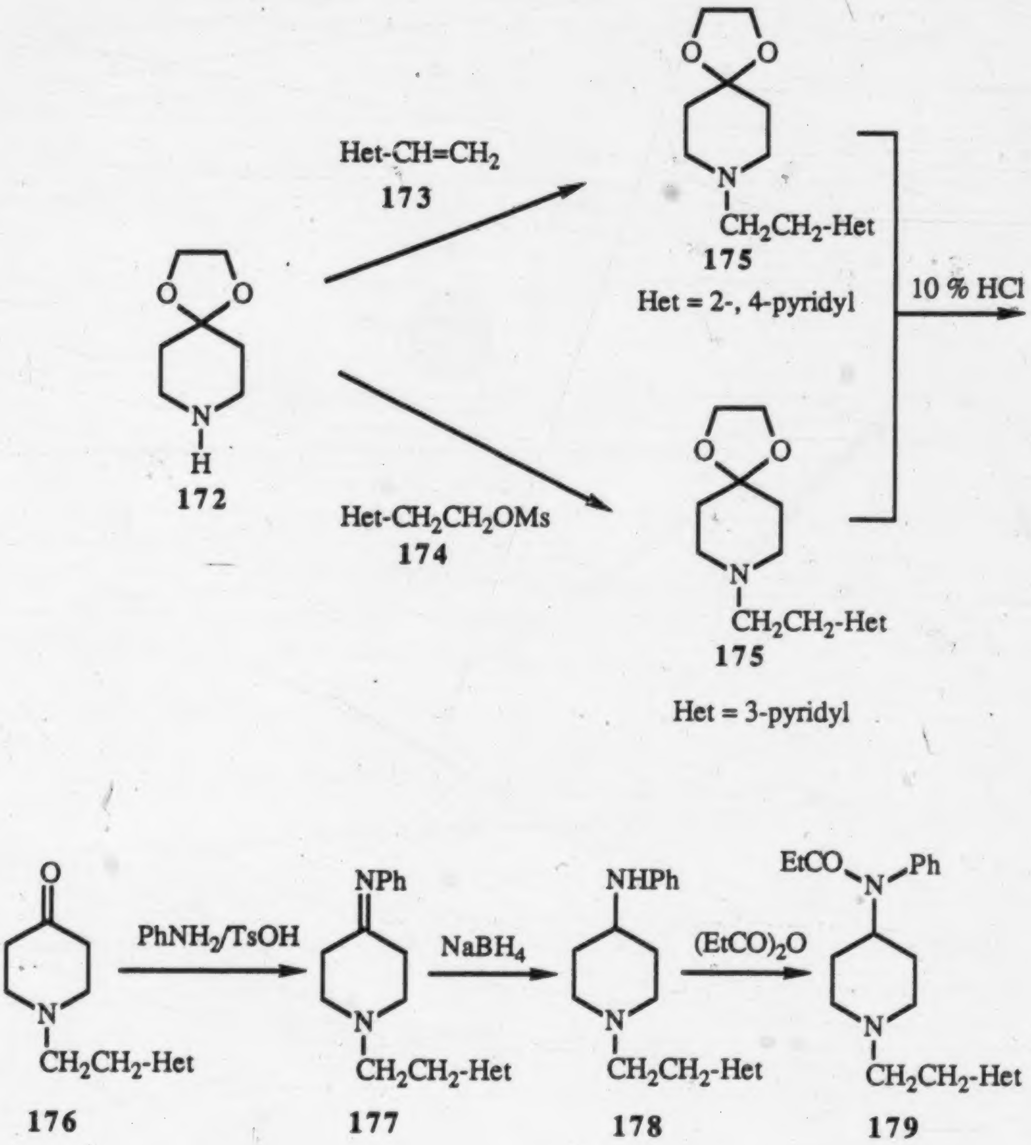
---

[a] No coalescence at 58 °C, but the resonance for the major peak shifted from δ 4.43 to δ 4.46 and that for the minor peak from δ 4.56 to δ 4.48.

[b] Incomplete coalescence.

3.2.7.0.0.0. Synthesis of 1-[2-(Pyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidines (179a-c)

The target compounds **179a-c** were synthesized to investigate the effect of replacement of the phenethyl "phenyl" group of fentanyl (**12a**) by a 2-, 3- and 4-pyridinyl ring system on analgesic activity. The 2-[313] and 4-pyridinyl [363] compounds **179a** and **c** have been previously synthesized. We now describe the synthesis of the 3-pyridinyl analog **179b** which was hitherto not reported. Various methods have been used to synthesize fentanyl and analogs thereof.[6] Most of these procedures involve reduction of a Shiff base, prepared by condensation of aniline or a substituted-aniline with 1-substituted-4-piperidones, followed by acylation of the anilino intermediate. This synthetic method was utilized in this study rather than an alternative procedure where the final product is synthesized by alkylation of the 1-H (NH) compound with an aralkyl halide.[313] The former pathway eliminates the possibility of intramolecular acyl migration from the anilido nitrogen to the piperidine nitrogen, which was reported recently by Colapret and co-workers [364] for the synthesis of a series of fentanyl analogs. The reaction sequence employed (Scheme 14) is similar to that recently reported by Fifer *et al*.[365]


Het-CH=CH$_2$
173
Het-CH$_2$CH$_2$OMs
174
172
175
Het = 2-, 4-pyridyl
175
Het = 3-pyridyl
10 % HCl
PhNH$_2$/TsOH
NaBH$_4$
(EtCO)$_2$O
NPh
NHPh
EtCO
Ph
CH$_2$CH$_2$-Het
176
177
178
179

a, Het = 2-pyridyl

b, Het = 3-pyridyl

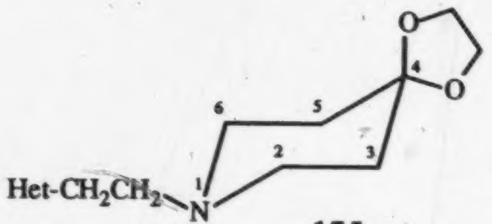
c, Het = 4-pyridyl

Scheme 14: Synthesis of 1-[2-(pyridyl)ethyl] analogs of fentanyl.

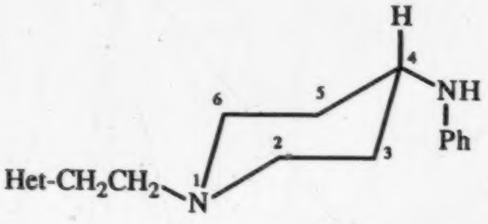
The 1,4-dioxa-8-azaspiro[4.5]decanes (**175a** and **c**, Het = 2-pyridyl and 4-pyridyl) were synthesized in 90 and 93 % yield respectively by the nucleophilic (Michael) addition of the 4-piperidone ketal **172** to 2- or 4-vinylpyridine (**173**) in refluxing methanol in the presence of the catalyst acetic acid. Katritzky and Rubio[366] reported that the nucleophilic Michael-type reaction of piperidine or pyrrolidine with 1-vinylpyridinium salts, required the presence of acetic acid to prevent polymerization which caused the reaction to fail. A similar reaction using 3-vinylpyridine failed to proceed to give the target product (**172b**). Magnus and Levine have reported that , in contrast to reactions using 2- and 4-vinylpyridine, 6-methyl-3-vinylpyridine did not undergo the Michael type nucleophilic addition reaction with piperidine.[367] The 3-pyridyl analog **179b** was therefore synthesized by a nucleophilic substitution reaction using the ketal **172** and the mesylate **174**. Compound **174** (Het = 3-pyridyl) was prepared by mesylation of 2-(3-pyridyl)ethanol, which was synthesized using a method similar to that reported by Kaiser and Petty.[368] Paraformaldehyde was added to 3-picolyl lithium in dry THF followed by refluxing to afford 2-(3-pyridyl)ethanol in 60 % yield. The physical and spectral data for compounds **179a-c** are summarized in Tables 22 and 23, respectively.

The IR spectra for compounds **179a**-**c** displayed a strong amide carbonyl absorption band in the 1655-1663 cm^{-1} range. The ^1H NMR spectra for **179a-c** exhibited chemical shifts for the H-4 proton in the δ 4.68-4.7 range which appeared as a triplet of a triplet with coupling constants of 3.5-4.5Hz and 11-12Hz. These characteristics for the H-4 resonance in the ^1H NMR spectrum of fentanyl have been interpreted to indicate that the solution conformation of fentanyl is a piperidine chair as illustrated in Fig. 14.[5, 75]

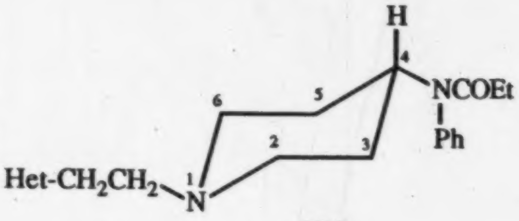
Table 22: Physical Data for Compounds **175**, **178** and **179**.


Het-CH$_2$CH$_2$
N
1
2
3
4
5
6
O
O

175


Het-CH$_2$CH$_2$
N
1
2
3
4
5
6
H
NH
Ph

178


Het-CH$_2$CH$_2$
N
1
2
3
4
5
6
H
NCOEt
Ph

179

Entry	Het	% Yield	MP, ^{o}C	Formula	Microanalysis: Calcd.(Found)		
					C	H	N
175a	2-pyridyl	90	42-43	$C_{14}H_{20}N_2O_2$	52.35(52.23)	6.90(6.94)	8.72(8.76)^a
175b	3-pyridyl	55	84-86	$C_{14}H_{20}N_2O_2$	67.72(67.45)	8.12(7.96)	11.28(11.30)
175c	4-pyridyl	93	70-71	$C_{14}H_{20}N_2O_2$	67.72(67.51)	8.12(7.93)	11.28(11.20)
178a	2-pyridyl	65	108-109	$C_{18}H_{23}N_3$	76.83(76.53)	8.23(8.36)	14.93(14.73)
178b	3-pyridyl	64	89-91	$C_{18}H_{23}N_3$	76.83(76.44)	8.23(8.07)	14.93(14.81)
178c	4-pyridyl	62	96-97	$C_{18}H_{23}N_3$	76.83(76.55)	8.23(8.40)	14.93(14.60)
179a	2-pyridyl	95	179-180^b	$C_{21}H_{28}N_3O$	67.45(67.24)	7.38(7.33)	11.24(11.11)^b
179b	3-pyridyl	97	92-93	$C_{21}H_{28}N_3O$	74.74(74.71)	8.06(8.22)	12.45(12.37)

179c	4-pyridyl	80	124-126	$C_{21}H_{28}N_3O$	74.74(74.77)	8.06(8.38)	12.45(14.73)

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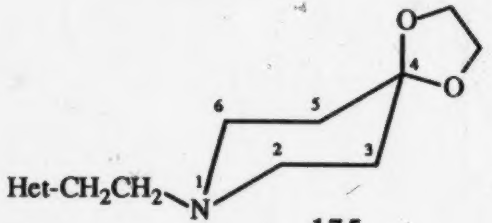
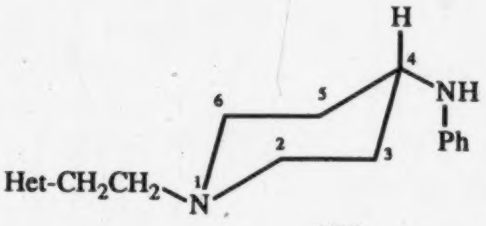
[a] Dihydrochloride salt.

[b] Monohydrochloride salt.

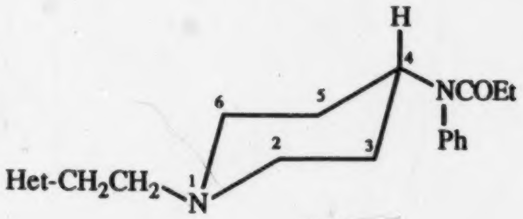
Table 23: IR and NMR Spectral Data for Compounds 175, 178 and 179.



175



178



179

Entry	Het	IR (KBr),cm^{-1}	NMR ($CDCl_3$), δ
175a	2-pyridyl	1089 (C-O)	^{1}H NMR: 1.72 (t, J = 6Hz, 4H, H-3,H-5), 2.6 (t, J = 6Hz, 4H, H-2, H-6), 2.75-3.06 (m, 4H, -CH_2CH_2-Pyr^b), 3.97 (s, 4H, O-CH_2CH_2-O), 7.03-7.27 (m, 2H, pyridine H-3, H-5), 7.6 (d, J = 8.5Hz of d, J = 8.5Hz, 1H, pyridine H-4), 8.5 (d, J = 6Hz, 1H, pyridine H-6).
175b	3-pyridyl	1089 (C-O)	^{1}H NMR: 1.78 (t, J = 6Hz, 4H, H-3, H-5), 2.64 (m, 6H, H-2, H-6, $CH_2$$CH_2$-Pyr), 2.82 (t, J = 7Hz, 2H, $CH_2$$CH_2$-Pyr), 4.0 (s, 4H, O-$CH_2CH_2$-O), 7.23 (d, J = 8Hz of d, J = 6Hz, 1H, pyridine H-5), 7.55 (d, J = 8Hz, 1H, pyridine H-4); 8.47 (m, 2H,

			pyridine H-2, H-6).
175c	4-pyridyl	1097 (C-O)	^{1}H NMR: 1.76 (t, J = 7Hz, 4H, H-3, H-5), 2.62-2.68 (m, 6H, H-2, H-6, $\mathrm{CH_2}\mathit{CH_2}$-Pyr), 2.8 (t, J = 7.5Hz, 2H, $\mathit{CH_2}$ $\mathrm{CH_2}$-Pyr), 3.97(s, 4H, O-$\mathit{CH_2CH_2}$-O), 7.14 (d, J = 6Hz, 2H, pyridine H-3, H-5) 8.51 (d, J = 6Hz, 2H, pyridine H-2, H-6)
178a	2-pyridyl	3312 (NH)	^{1}H NMR: 1.52 (d, J = 4Hz of d, J = 11Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-3ax, H-5ax), 2.12 (br d, J =11Hz, 2H, H-3eq, H-5eq), 2.28 (d, J = 4Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-2ax, H-6ax), 2.84 (d, J = 6Hz of d,J = 10Hz, 2H, $\mathrm{CH_2}\mathit{CH_2}$-Pyr), 3.0-3.08 (m, 4H, H-2eq, $\mathit{CH_2}\mathrm{CH_2}$Pyr), 3.34 (m, 1H, H-4), 3.56 (br s, 1H, NH, exchanges with deuterium oxide), 6.66 (d, J = 9Hz, 2H, *o*-phenyl hydrogens), 6.74 (t, J = 9 Hz, 1H, *p*-phenyl hydrogens), 7.08-7.14 (m, 4H, pyridine H-3, H-5,*m*-phenyl hydrogens), 7.66 (d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.58 (d, J = 6Hz, 1H pyridine H-6).
178b	3-pyridyl	3267 (NH)	^{1}H NMR: 1.5 (d, J = 4Hz of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-3ax, H-5ax), 2.1 (br d, J =12 Hz, 2H, H-3eq, H-5eq), 2.25 (d, J = 12Hz of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.64 (t, J = 7Hz, 2H, $\mathrm{CH_2}\mathit{CH_2}$-Pyr), 2.83 (t, J = 7Hz, 2H,

			$\mathit{CH_2}$ CH_2-Pyr), 2.98 (br d, J = 12Hz, 2H, H-2eq), 3.34 (m, 1H, H-4), 3.56 (br s, 1H, NH, exchanges with deuterium oxide), 6.62 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 6.70 (t, J = 8Hz, 1H, *p*-phenyl hydrogen), 7.18-7.24 (m, 3H, *m*-phenyl hydrogens, pyridine H-5), 7.55 (d, J = 2Hz of d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.49 (m, 2H, pyridine H-2, H-6).
178c	4-pyridyl	3295 (NH)	^{1}H NMR: 1.5 (d, J = 4Hz of d, J = 11Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-3ax, H-5ax), 2.12 (br d, J = 11Hz, H-3eq, H-5eq), 2.24 (d, J = 4Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-2ax, H-6ax), 2.66 (d, J = 6Hz of d, J = 10Hz, 2H, $CH_2\mathit{CH_2}$-Pyr), 2.83 (d, J = 6Hz of d, J = 10 Hz, 2H, $\mathit{CH_2}CH_2$-Pyr), 2.98 (br d, J = 11Hz, 2H, H-2eq, H-6eq), 3.36 (m, 1H, H-4), 3.56 (br s, 1H, NH, exchanges with deuterium oxide), 6.4 (d, J = 9Hz, 2H, *o*-phenyl hydrogens), 6.72 (t, J = 9Hz, 1H, *p*-phenyl hydrogen), 7.2 (m, 4H, pyridine H-3, *m*-phenyl hydrogens), 8.55 (d, J = 6Hz, 2H, pyridine H-2).
179a	2-pyridyl	1655 (C=O)	^{1}H NMR: 1.0 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.42 (d, J = 4Hz of d, J = 11Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-3ax, H-5ax), 1.8 (br d, J = 11Hz, 2H, H-3 eq, H-5eq), 1.92 (q, J = 7Hz, 2H, $\mathit{CH_2}CH_3$), 2.2 (d, J = 4Hz of d, J = 11Hz of d, J =

			11Hz, 2H, H-2ax, H-6ax), 2.72 (d, J = 6Hz of d, J = 10Hz, 2H, $CH_2\mathit{CH_2}$-Pyr), 2.92 (d, J = 6Hz of d, J = 10Hz, 2H, $\mathit{CH_2}CH_2$-Pyr), 3.0 (br d, J = 11Hz, 2H, H-2eq), 4.68 (t, J = 4Hz of t, J = 11Hz, 1H, H-4), 7.14 (m, 4H, phenyl hydrogens), 7.4 (m, 3H, phenyl hydrogen, pyridine H-3, H-5), 7.6 (t, J = 7Hz, 1H, pyridine H-4), 8.52 (d, J = 4Hz, 1H, pyridine H-6). ^{13}C NMR: 9.56 ($CH_2\mathit{CH_3}$), 28.45 (C-3, C-5), 30.51 ($\mathit{CH_2}CH_3$), 35.84 ($CH_2\mathit{CH_2}$-Pyr), 52.22 (C-4), 53.0 (C-2, C-6), 58.24 ($\mathit{CH_2}CH_2$-Pyr), 121.1(pyridine C-3), 123.04 (pyridine C-3), 128.20 (phenyl C- 4), 129.24 (phenyl C-3, C-5), 130.38 (phenyl C-2, C-6), 136.25 (pyridine C-4), 138.97 (phenyl C-1), 149.24 (pyridine C-6), 160.27 (pyridine C-2), 173.48 (C=O).
179b	3-pyridyl	1663 (C=O)	^{1}H NMR: 1.02 (t, J = 7.5Hz, 3H, $CH_2\mathit{CH_3}$), 1.4 (d, J = 3.5Hz of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-3ax, H-5ax), 1.81 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.93 (q, J = 7.5Hz, 2H, $\mathit{CH_2}CH_3$), 2.18 (d, J = 3.5Hz of d, J = 12 Hz of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.52 (d, J = 6Hz of d, J = 10Hz, 2H, $CH_2\mathit{CH_2}$-Pyr), 2.7 (d, J = 6Hz of d, J = 10Hz, 2H, $\mathit{CH_2}CH_2$-Pyr), 2.98 (d, J =11.5Hz, 2H, H-2 eq, H-6eq), 4.69 (t, J = 3.5Hz of t, J = 12Hz, 1H, H-4), 7.08 (m, 2H, *o*-phenyl

			hydrogens), 7.16 (d, J = 6Hz of d, J = 7.8Hz, 1H, pyridine H-5), 7.33-7.48 (m, 3H, *m*- and *p*-phenyl hydrogens), 7.46 (d, J = 7.8Hz, 2H, pyridine H-4), 8.42-8.44 (m, 2H, pyridine H-2, H-6). ^{13}C NMR: 9.55 ($\mathrm{CH_2}CH_3$), 28.47 (C-3, C-5), 30.57 ($CH_2\mathrm{CH_3}$), 30.90 ($\mathrm{CH_2}CH_2$-Pyr), 52.20 (C-4), 53.07 (C-2, C-6), 59.71 ($CH_2\mathrm{CH_2}$-Pyr), 123.19 (pyridine C-5), 128.24 (phenyl C-4), 129.27 (phenyl C-3, C-5), 130.38 (phenyl C-2, C-6), 135.64 (pyridine C-3), 135.92 (pyridine C-4), 138.94 (phenyl C-1), 147.54 (pyridine C-6), 150.08 (pyridine C-2),173.48 (C=O).
179c	4-pyridyl	1655 (C=O)	^{1}H NMR: 1.0 (t, J = 7Hz, 3H, $\mathrm{CH_2}CH_3$), 1.4 (d, J = 4.5 Hz of d, J = 11Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-3ax, H-5ax), 1.82 (br d, J = 11Hz, 2H, H-3eq, H-5eq), 1.94 (q, J = 7Hz, 2H, $CH_2\mathrm{CH_3}$), 2.18 (d, J = 4.5Hz of d, J = 11Hz of d, J = 11Hz, 2H, H-2ax, H-6ax), 2.54 (d, J = 6Hz of d, J = 10Hz, 2H, $\mathrm{CH_2}CH_2$-Pyr), 2.72 (d, J = 6Hz of d, J = 10Hz, 2H, $CH_2\mathrm{CH_2}$-Pyr), 3.0 (br d, J = 11Hz, 2H, H-2eq, H-6eq), 4.72 (t, J = 4.5Hz of t, J = 11Hz, 1H, H-4), 7.14 (m, 4H, *o*- and *m*-phenyl hydrogens), 7.42 (m, 3H, *p*-phenyl hydrogen, pyridine H-3, H-5), 8.5 (d, J = 6Hz, 2H, pyridine H-2, H-6).

^{13}C NMR: 9.49 ($CH_2\mathit{CH_3}$), 28.47 (C-3, C-5), 30.47 ($\mathit{CH_2}CH_3$), 32.6 ($CH_2\mathit{CH_2}$-Pyr), 52.06 (C-4), 52.92 (C-2, C-6), 58.66 ($\mathit{CH_2}CH_2$-Pyr), 124.09 (pyridine C-3, H-5), 128.31 (phenyl C-4), 129.30 (phenyl C-3, C-5), 130.35 (phenyl C-2, C-6), 138.88 (phenyl C-1), 149.42 (pyridine C-2, C-6), 150.0 (pyridine C-4), 173.60 (C=O).

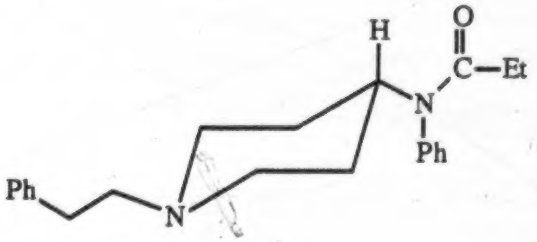
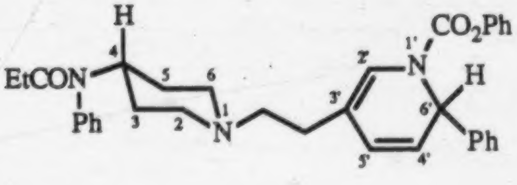


Fig 14: Solution conformation of fentanyl.

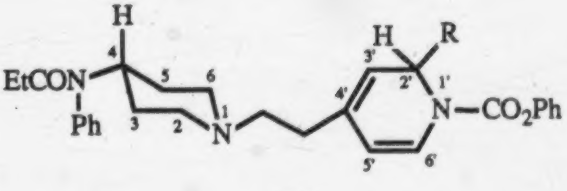
The ^{13}C NMR spectra for compounds **179a-c** (Table 21) were similar to the ^{13}C NMR spectra for fentanyl and analogs thereof that were recently reported.[369] This spectral similarity indicates that compounds **179a-c** possess solution conformations similar to fentanyl and related analogs.

3.2.7.1.0.0. Synthesis of 1-[2-(1-phenoxycarbonyl-1,6-(1,2) dihydropyridyl)ethyl]-4-[(N-phenyl-N-propionyl)amino]piperidines (180 and 181a-d)

The addition reactions of Grignard reagents with pyridinium salts and $NaBH_4$ reduction procedures described previously were applied to the N-phenoxycarbonylpyridinium chlorides of compounds **179b** and **c** to prepare the 1,6- and 1,2-dihydropyridine analogs **180** and **181a-d**, respectively, in 38-59 % yields. The regiospecific reaction of the 3-pyridyl compound **179b** with phenyl chloroformate and phenylmagnesium chloride at -78 ^{o}C afforded the 1,6-dihydropyridine product **180**. The absence of the 1,2-dihydropyridine product is attributed to steric hindrance which prevents attack at C-2' of the intermediate pyridinium salt. The physical and spectral data for compounds **180** and **181a-d** are summarized in Tables 24 and 25, respectively.

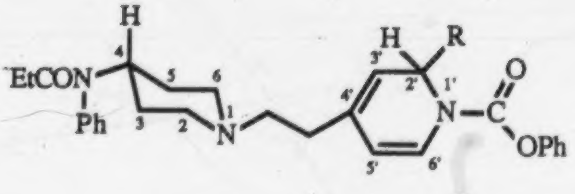


180

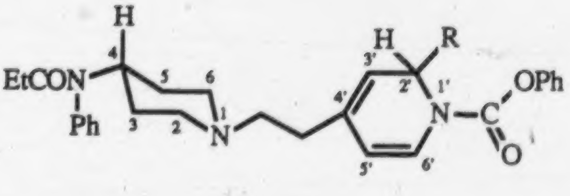


181

The presence of rotamers in the dihydropyridines **181** was indicated by the appearance of dual resonance peaks in their ^{1}H NMR spectra, recorded at 25 ^{o}C. Rotamers occurred because of the presence of the carbamate moiety as discussed previously for compounds **152-154, 169** and **171**. The two rotameric configurations for compounds **181a-d** are represented by structures **I** and **J** below. Dual resonances were observed predominantly with the C-2' unsubstituted (**181a**) or alkyl-(Me, *n*-Bu)substituted (**181b-c**) compounds.



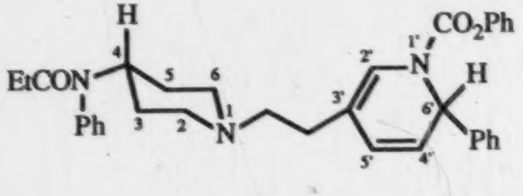
I



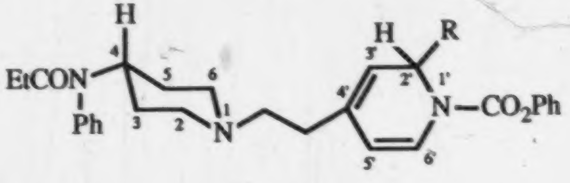
J

As discussed previously, the electron-withdrawing Ph substituent disfavors rotational isomerism by lowering the energy barrier to rotation. For compounds **181a-c** the following dihydropyridine protons exhibited dual resonances at 25 °C: H-2', H-5' and H-6'. The C-2' Me of compound **181b** also exhibited dual resonances peaks. For the C-2' phenyl-substituted compound (**181d**), only the H-6' proton exhibited dual resonances. The following rotameric ratios were observed: **181a**, 5 : 3 (H-6' peaks); **181b**, 3 : 2 (C-2' Me peaks); **181c**, 6 : 5 (H-5' peaks) and **181d**, 2 : 1 (H-6' peaks). At 58 °C the H-5' and H-6' dual peaks for compound **181a** coalesced whereas the H-2' peaks exhibited incomplete coalescence at this temperature. All the dual resonance peaks of compound **181b** exhibited incomplete coalescence at 58 °C. For compound **181c** the H-6' dual peaks coalesced at 58 °C, but the H-2' and H-5' dual resonances exhibited only partial coalescence at this temperature. The H-6' dual resonances for compound **181d** coalesced at 58 °C.

Talble 24: Physical Data for Dihydropyridinyl analogs **180** and **181a-d**.


H
4
5
6
EtCON
Ph
3
2
1
N
2'
1'
N
CO2Ph
H
3'
6'
Ph
5'
4'

180


H
4
5
6
EtCON
Ph
3
2
1
N
H
R
3'
2'
1'
4'
N—CO2Ph
5'
6'

181

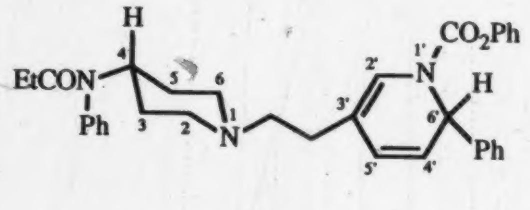
Entry	R	% Yield	MP, °C	Formula	Microanalysis: Calcd.(Found)			Exact Mass	
					C	H	N	Calcd.	Found
180	Ph	57	oil	$C_{34}H_{37}N_3O_3$				535.2853	245.1654[a]
181a	H	59	128-129	$C_{28}H_{33}N_3O_3$	73.18(73.19)	7.24(7.19)	9.14(9.16)		
181b	me	39	oil	$C_{29}H_{35}N_3O_3$				473.2678	473.2690
181c	*n*-Bu	46	oil	$C_{32}H_{41}N_3O_3$				513.3148	245.1653[a]
181d	Ph	38	oil	$C_{34}H_{37}N_3O_3$	52.12(52.23)	5.33(4.97)	5.47(5.49)[b]		

---

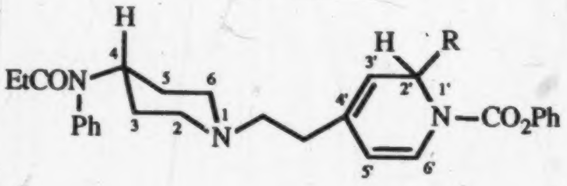
[a] Base peak ($C_{23}H_{21}N_2O$); calcd. 245.1599.

[b] Calculated for the hexachloroplatinic acid salt ($C_{68}H_{76}N_6O_6Cl_6Pt.3H_2O$).

Table 25: IR and ^{1}H NMR Spectral Data for Compounds **180** and **181a-d**.


H
EtCON
Ph
4
5
6
3
2
1
N
3'
2'
1'
N
CO2Ph
H
6'
Ph
5'
4'

180


H
EtCON
Ph
4
5
6
3
2
1
N
4'
3'
H
2'
R
1'
N—CO2Ph
5'
6'

181

Entry	R	IR, cm^{-1}	^{1}H NMR (CDCl$_3$), δ
180	Ph	1725 (C=O), 1655 (C=O)	58 °C: 1.03 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.44 (d, J = 5Hz of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-3ax, H-5ax), 1.8 (m, 2H, H-3eq, H-5eq), 1.92 (q, J = 7Hz, 2H, $\mathit{CH_2}CH_3$), 2.15 (m, 2H, H-2ax, H-6ax) 2.28 (t, J = 7Hz, $CH_2\mathit{CH_2}$-DHP^a), 2.46 (t, J = 7Hz, 2H, $\mathit{CH_2}CH_2$-DHP), 2.98 (br d, J = 12Hz, 2H, H-2eq, H-6eq), 4.66 (m, 1H, H-4), 5.7 (d, J = 6Hz, of d, J = 8Hz, H-5'), 5.9 (d, J = 6Hz, 1H, H-6'), 6.0 (m, 1H, H-4'), 6.7 (s, 1H, H-2'), 7.1 - 7.46 (m, 15H, OPh, Ph).

181a	H	1721(C=O), 1655 (C=O)	25 ^{o}C: 1.02 (t, J = 7Hz, 3H, $\mathrm{CH_2}CH_3$), 1.4 (d, J = 4Hz of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-3ax, H-5ax), 1.8 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.93 (q, J = 7Hz, $CH_2\mathrm{CH_3}$), 2.1-2.2 (m, 4H, H-2ax, H-6ax, $\mathrm{CH_2}CH_2$-DHP), 2.4 (d, J = 6Hz of d, J = 10Hz, 2H, $CH_2\mathrm{CH_2}$-DHP), 2.92 (br d, J = 12Hz, 2H, H-2eq, H-6eq), 4.38[4.52] (d, J = 3Hz, 2H, H-2'), 4.67 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 5.12[5.16] (d, J = 8Hz, 1H, H-5'), 5.28 (m, 1H, H-3'), 6.86[6.79] (d, J = 8Hz, 1H, H-6'), 7.06 - 7.12 (m, 4H, *o*-phenyl hydrogens), 2.75 (m, 2H, *p*-phenyl hydrogens), 7.38 (m, 4H, m-phenyl hydrogens). Rotameric ratio = 3 : 5 (H-6' peaks). 58^{o}C: 1.02(t, J =7Hz, 3H, $\mathrm{CH_2}CH_3$),1.42 (d,J =12Hz of d, J =12Hz of d, J =12Hz, 2H, H-3ax, H-5ax), 1.78 (m, 2H, H-3eq, H-5eq), 1.93 (q, J = 7Hz, 2H, $CH_2\mathrm{CH_3}$), 2.08-2.18 (m, 4H, H-2ax, H-6ax, $\mathrm{CH_2}CH_2$-DHP), 2.4 (d, J = 6Hz of d , J = 10Hz, 2H, $CH_2\mathrm{CH_2}$DHP), 2.92 (br d, J = 12Hz, 2H, H-2eq, H-6eq), 4.39-4.48 (m, 2H, H-2'), 4.65 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 5.15 (d, J = 8Hz, 1H, H-5'), 5.28 (m, 1H, H-3'), 6.83 (d, J = 8Hz, 1H, H-6'), 7.08-7.12 (m, 4H, *o*-phenyl hydrogens), 7.18-7.22 (m, 2H, *p*-phenyl hydrogens), 7.34-7.4 (m, 4H, *m*-phenyl hydrogens).

181b	Me	1721 (C=O), 1649 (C=O)	25 °C: 1.02 (t, J = 7Hz, 3H, $\mathrm{CH_2CH_3}$), 1.16[1.24] (d, J = 7Hz, 3H, C-2' Me), 1.4 (d, J = 4Hz of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H, H-3ax, H-5ax), 1.8 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.93 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 2.18 (t, J = 12Hz, 2H, H-2ax, H-6ax), 2.23 (m, 2H, H-2ax, $\mathrm{CH_2}\mathit{CH_2}$-DHP), 2.4 (m, 2H, $\mathit{CH_2}\mathrm{CH_2}$-DHP), 2.95 (br d, J = 12Hz, 2H, H-2eq, H-6eq), 4.68 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 4.84[4.91] (m, 1H, H-2'), 5.19[5.25] (d, J = 8Hz, 1H, H-5'), 5.31 (d, J = 6Hz, 1H, H-3'), 6.79[6.72] (d, J = 8Hz, 1H, H-6'), 7.07 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.13 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.23(t, J = 8Hz, 1H, *p*-phenyl hydrogens), 7.4 (m, 5H, *m*- and *p*-phenyl hydrogens). Rotameric ratio = 3 : 2 (C-2' Me peaks). 58°C: 1.02 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.2 (d, J = 7Hz, 3H, C-2' Me), 1.42 (d, J = 4Hz of J =12Hz of d J =12Hz of d, J =12Hz, 2H, H-3ax, H-5ax), 1.79 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.96 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 2.1-2.2 (m, 4H, H-2ax, H-6ax, $\mathrm{CH_2}\mathit{CH_2}$-DHP), 2.42 (t, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_2}$-DHP), 2.94 (m, 2H, H-2eq, H-6eq), 4.65 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 4.87 (m,

			1H, H-2'), 5.2 (d, J = 8Hz, 1H, H-5'), 5.3 (d, J = 6Hz, 1H, H-3'), 6.76 (d, J = 8Hz, 1H, H-6'), 7.06-7.24 (m,6H, *o*- and *p*-phenyl hydrogens),7.32-7.42 (m, 4H, *m*-phenyl hydrogens).
181c	n-Bu	1729(C=O), 1655(C=O)	25 °C: 0.88 (t, J = 7Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.01 (t, J = 7Hz, 3H,CH_2CH_3), 1.26 - 1.3 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.4 (d, J = 4Hz, of d, J = 12Hz of d, J = 12Hz of d, J = 12Hz, 2H,H-3ax, H-5ax), 1.5-1.66 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.8 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.94 (q, J = 7Hz, 2H, CH_2CH_3), 2.13 (d, J = 12Hz of d, J = 12Hz, 2H, H-2ax, H-6ax), 2.2 (t, J = 7.2Hz, 2H, CH_2CH_2-DHP), 2.4 (t, J = 7.2Hz, 2H, CH_2CH_2-DHP), 2.95 (d, J = 12Hz, 2H, H-2eq, H-6eq), 4.68 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 4.73[4.81] (m, 1H, H-2'), 5.2-5.27 (d, J = 8Hz, 1H, H-5'), 6.81[6.74] (d, J = 8Hz, 1H, H-6'), 7.08 (d, J = 2Hz of d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.13 (d, J = 8Hz, 2H, *o*-phenyl hydrogens), 7.22 (t, J = 8Hz, 1H, *p*-phenyl hydrogens), 7.38 (m, 5H, *m*- and *p*-phenyl hydrogens). Rotameric ratio = 6 : 5 (H-5' peaks). 58 °C: 0.88(m, 3H, $CH_2CH_2CH_2CH_3$), 1.01(t, J = 7Hz, 3H, CH_2CH_3), 1.26-1.7 (m, 8H, $CH_2CH_2CH_2CH_3$, H-3ax, H-5ax), 1.8 (br d, J =12Hz, 2H, H-3eq,

			H-5eq), 1.94 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 2.1-2.24 (m, 4H, $\mathrm{CH_2}\mathit{CH_2}$-DHP, H-2ax, H-6ax), 2.42 (t, J = 7.2Hz, 2H, $\mathit{CH_2}\mathrm{CH_2}$Pyr), 2.9 (br d, J =12Hz, 2H, H-2eq, H-6eq), 4.64 (t, J = 4Hz of t, J = 12Hz, 1H, H-4), 4.78 (m, 1H, H-2'), 5.24 (m, 1H, H-5'), 5.36 (d, J = 6Hz, 1H, H-3'), 6.78 (d, J = 8Hz, 1H, H-6'), 7.08-7.24 (m, 6H, *o*- and *p*-phenyl hydrogens), 7.36-7.4 (m, 4H, *m*-phenyl hydrogens).
181d	Ph	1720(C=O), 1655 (C=O)	25 °C: 1.02 (t, J = 7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.4 (m, 2H, H-3ax, H-5ax), 1.78 (m, 2H, H-3eq, H-5eq), 1.93 (q, J = 7Hz, 2H,$\mathit{CH_2}\mathrm{CH_3}$), 2.13 (m, 2H, H-2ax, H-6ax), 2.27 (m, 2H, $\mathrm{CH_2}\mathit{CH_2}$-DHP), 2.46 (m, 2H, $\mathit{CH_2}\mathrm{CH_2}$-DHP), 2.95 (m, 2H, H-2eq, H-6eq), 4.67 (m, 1H, H-4), 5.28 (d, J = 8Hz, 1H, H-5'), 5.45 (m, 1H, H-3'), 5.88 (d, J = 6Hz, 1H, H-2'), 6.92[6.88] (d, J = 8Hz, 1H, H-6'), 7.08 (m, 2H, *o*-phenyl hydrogens), 7.2-7.46 (m, 13H, *o*-, *p*- and *m*-phenyl hydrogens). Rotameric ratio = 5 : 1 (H-6' peaks). 58 °C: 1.01 (t, J =7Hz, 3H, $\mathrm{CH_2}\mathit{CH_3}$), 1.4 (m, 2H, H-3ax, H-5ax), 1.78 (br d, J = 12Hz, 2H, H-3eq, H-5eq), 1.95 (q, J = 7Hz, 2H, $\mathit{CH_2}\mathrm{CH_3}$), 2.1-2.3 (m, 2H, H-2ax, H-6ax, $\mathrm{CH_2}\mathit{CH_2}$DHP), 2.46 (m, 2H, $\mathit{CH_2}\mathrm{CH_2}$-DHP), 2.95 (br d, J =

12Hz, 2H, H-2eq, H-6eq), 4.64 (m, 1H, H-4), 5.28 (d, J = 8Hz, 1H, H-5'), 5.45 (m, 1H, H-3'), 5.88 (d, J = 6Hz, 1H, H-2'), 6.9 (d, J = 8Hz, 1H, H-6'), 7.07 (m, 2H, *o*-phenyl hydrogens), 7.2-7.46 (m, 13H, *o*-, *p*- and *m*- phenyl hydrogens).

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[a] DHP = Dihydropyridine ring.

[b] Chemical shift value in square brackets is that for the corresponding resonance in the minor rotameric product.

3.3.0.0.0.0. PHARMACOLOGY

3.3.1.0.0.0. Antinociceptive Evaluation

Chemically induced animal writhing assays are common protocols used for antinociceptive (analgesic) evaluation. These screens are simple, and in general animal potency is directly proportional to clinical potency observed in man.[370] The phenylquinone-induced writhing test in mice is the most extensively used writhing assay. However a serious limitation with this test is the exhibition of false positives for some classes of compounds[371] for example tranquilizers such as chlorpromazine. Since repeated challenges using phenylquinone at short intervals are not possible, the time course of drug action cannot be determined. Chronic phenylquinone challenges may also cause damage to abdominal organs.

The hypertonic sodium chloride-induced writhing assay in rats, the protocol which was used for the antinociceptive evaluation in this investigation, has been reported to be highly specific with no incidence of false positives.[372] Hypertonic sodium chloride solution (4 % w/v, 1 M) was found to be the most reliable agent from a number of nociceptive agents evaluated for this purpose in rats.[373] The 4 % sodium chloride-induced writhing assay also has the advantages that repeated challenges at short intervals (15 minutes) are possible and chronic challenges do not cause damage to abdominal organs.[372] The percentage reduction in writhing responses (% inhibition) caused by the test compounds as compared to control responses was used as a measure of antinociceptive (analgesic) activity.

3.3.1.0.0.0. Analgesic Activity of 1,2,3,6-, 1,2,5,6-Tetrahydropyridylidene-(134a-h, 143a-g) and Piperidylidene-2-aryloxysulfonamides (144a-h)

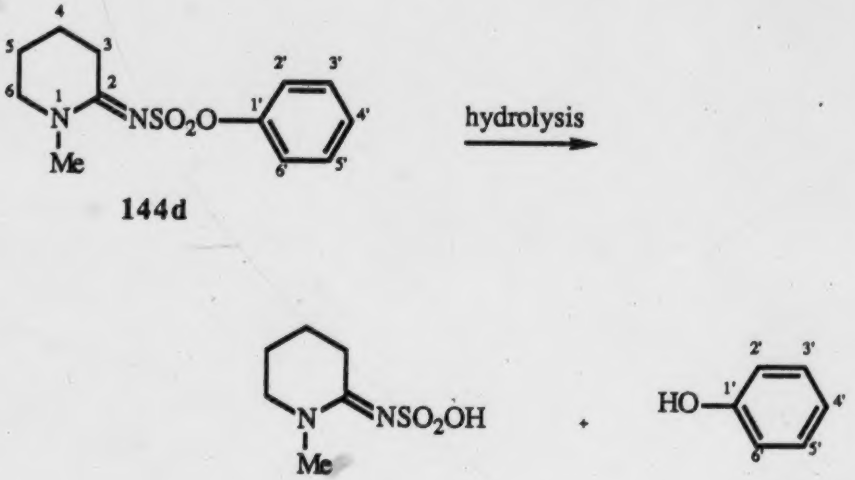
The three structurally related classes of compounds **134a-h**, **143a-g** and **144a-h** were investigated to determine the effect which insertion of an oxygen spacer between the sulfonyl sulfur atom and the aromatic ring of the novel 1-substituted-piperidylidene-2-arylsulfonamides **124**, had on analgesic activity. The effects which the position of the double bond in the 1,2,3,6-tetrahydropyridylidene- and 1,2,5,6-tetrahydropyridylidene-2-aryloxysulfonamides **134a-h** and **143a-g** and a C-6 alkyl (Me, *n*-Bu), phenyl or hydrogen substituent in compounds **134a-h**, **143a-g** and **144a-h** had on analgesic activity were also investigated.

3.3.1.1.0.0. Structure-activity relationships

The analgesic test results in Table 6 indicate that the piperidylidene-2-aryloxysulfonamides of general structure **144** were generally more active than the 1,2,5,6-tetrahydropyridylidene-2-aryloxysulfonamides of general structure **143** which in turn were more active than the 1,2,3,6-tetrahydropyridylidene-2-aryloxysulfonamides of general structure **134**. The one exception to this generalization arose in the comparison of **143e** ($R^1 = R^2 =$ Me, Ar = Ph) with **144e** ($R^1 = R^2 =$ Me, Ar = Ph), where the activity of compound **143e** was not unequivocally different ($0.1 > p > 0.05$, Student t Test) from that of compound **144e**. No consistent correlation was observed which would indicate a difference in activity between N-unsubstituted versus N-methyl compounds in the three series of compounds (**134**, **143** and **144**). Substituents in the C-6 position such as Me, *n*-Bu or Ph usually enhanced analgesic activity relative to the C-6 unsubstituted compound; the test results showed ($p < 0.05$) the following activity profile : *n*-Bu (**134f**) > H (**134d**); Me (**143e**) >H (**143d**); Ph (**143g**) > H (**143d**); *n*-Bu (**144f**) > H (**144d**) and Ph (**144g**) > H (**144d**).

The low activity exhibited by compounds **134a-h**, **143a-g** and **144a-h** at 50 mg/kg sc, relative to the μ-receptor agonists, meperidine (ED_{50} = 0.6 mg/kg sc) and morphine (ED_{50} = 0.09 mg/kg sc), is highly suggestive that the former compounds do not interact with the μ-receptor or act as μ-receptor agonists at the dose tested. This implies that the oxygen spacer in the aryloxysulfonamides **134**, **143** and **144** is detrimental to analgesic activity relative to the arylsulfonamides **124** where the sulfonyl sulfur atom is bonded directly to the aromatic ring.[291] Studies with opioid antagonists such as naloxone would indicate whether these new aryloxysulfonamides interact with opioid receptors.

The aryloxysulfonamide series **134**, **143** and **144** are sulfamic acid esters. They are stable compounds *in vitro*. However *in vivo* cleavage by hydrolases could be a determinant, at least in part, for their reduced analgesic activity as depicted for compound **144d** below (Eq. 30).



144d

Eq. 30

145

phenol

This hydrolysis could be minimized by introducing bulky substituents such as *t*-butyl or perhaps methyl (compare lidocaine) at the C-2' and C-6' positions of compound **144d**. Such a modification would be expected to hinder access of the hydrolases to the sulfamic ester moiety. *In vivo* studies with opioid antagonists such as naloxone and *in vitro* receptor binding studies would be required to determine whether compounds **134**, **143** and **144** interact with opioid receptors, and if so which types of opioid receptors.

Compounds **134**, **143**, **144** do not appear to be toxic (acute toxicity) to rats at 50 mg/kg sc, since no apparent external changes were observed in the rats used for the analgesic testing.

The 6-alkyl (or phenyl) substituted compounds were tested as racemates. Although we are aware that enantioselectivity is relevant to ligand-opioid receptor interactions, the low activity exhibited by these compounds did not warrant the separation of enantiomers.

3.3.2.0.0.0. Analgesic Activity of 1-Methylpiperidylidene-2-(pyridyl)sulfonamides (150a-c)

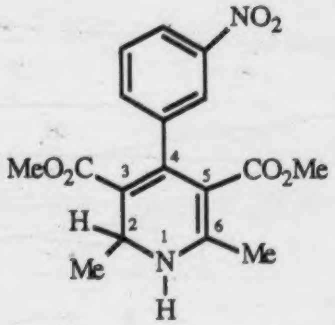
The test results summarized in Table 8 indicate that the piperidylidene-2-(pyridyl)sulfonamides **150a-c** exhibited low analgesic activity compared to morphine and meperidine in the rat sodium chloride-induced writhing test. This difference in analgesic activity may be due to the differences between the piperidine ring conformation of the piperidylidene-2-(pyridyl)sulfonamides (**150a-c**) and that of the clinically used opioid analgesics such as morphine and meperidine. The piperidine ring present in morphine and meperidine is reported to adopt a chair conformation is solution.[113] The ^{1}H NMR data for the 1-methylpiperidylidene-2-sulfonamides (**150a-c**) summarized in Table 7 indicate that the piperidine ring present in these compounds may not adopt a chair conformation, at least in chloroform solution. This is because of the fact that the ^{1}H NMR data do not indicate axial and equatorial proton coupling constants (J values) characteristic of piperidine chair conformations, where geminal proton (J_{gem} = 11-13Hz), vicinal axial/axial ($J_{ax,ax}$ = 10-

12Hz), vicinal axial/equatorial ($J_{ax,eq}$ = 2-6Hz) and vicinal equatorial/equatorial ($J_{eq,eq}$ = 2-3Hz) couplings are observed.

The test results indicated that at a dose of 6.25 mg/kg sc, the 2-pyridyl compound **150a**, which exhibited 58.2 ± 7.5 % inhibition was 1.5 times more potent than the 3-pyridyl isomer **150b**, which exhibited 39.0 ± 3.7 % inhibition ($p = 0.05$). The 4-pyridyl isomer **150c** was equiactive (57 ± 6.0 % inhibition) with the 2-pyridyl compound **150a**. These results imply that the pyridine ring nitrogen position is an important determinant of analgesic activity for isomeric 1-methylpiperidylidene-2-(pyridyl)sulfonamides (**150a-c**). The relative order of potency was 2-pyridyl (**150a**) = 4-pyridyl (**150c**) > 3-pyridyl (**150b**). These differences in analgesic activity could be due to electronic and/or steric effects. The analgesic testing was done *in vivo* and therefore differences in pKa and partition coefficients would affect the quantity of test compound reaching the active sites. It has been reported [291] that there is no apparent correlation between the analgesic potency of 1-methylpiperidylidene-2-benzenesulfonamides (**124**) and hydrophobic (π) or electronic (σ) parameters. Based on the structure-activity relationships acquired for the 1,2,3,6-tetrahydropyridylidene-, 1,2,5,6-tetrahydropyridylidene- and piperidylidene-2-aryloxysulfonamides, **134**, **143** and **144**, respectively (section **3.3.2.1.0.0**), incorporation of an alkyl (Me, *n*-Bu) or a phenyl substituent at the C-6 position of 1-methylpiperidylidene-2-(pyridyl)sulfonamides **150a-c** may enhance analgesic activity.

3.3.2.1.0.0. Analgesic activity of 1-methylpiperidylidene-2-(1-phenoxycarbonyl-1,6(1,2)-dihydropyridyl)sulfonamides (152a-d and 154a-e)

Compounds **152** and **154** were synthesized to investigate the bioisosteric relationship between the pyridine ring present in 1-methylpiperidylidene-2-(pyridine)sulfonamides **150b, c** and the dihydropyridine ring system present in 1-methylpiperidylidene-2-(1-phenoxycarbonyl-1,6(1,2)-dihydropyridyl)sulfonamides **152a-d** and **154a-e**. Reduction of the pyridine ring in 4-(pyridyl) analogs of nifedipine to the dihydropyridine ring system has been shown to enhance calcium channel blocking activity.[349] The X-ray crystallographic structure of the 1,2-dihydropyridine compound **182** indicated that the five atoms N-1, C-6, C-5, C-4 and C-3 form a reasonably flat plane.[374]



182

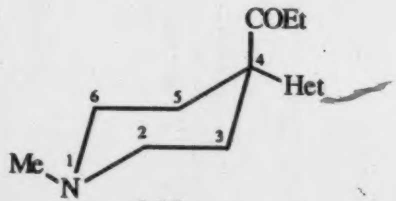
It was therefore envisaged that the 1,6- or 1,2-dihydropyridine ring present in compounds **152a-d** and **154a-e**, respectively could bind to a flat region on the opioid receptor as proposed by Beckett and Casy.[110] The dihydropyridine analogs **152a-d** and **154a-e** might also serve as prodrugs for the pyridine compounds **150b, c** since *in vivo* hydrolysis and aromatization may occur. The enhanced lipophilicity of the dihydropyridine relative to the pyridine compounds may also enhance drug transport across the blood-brain barrier.[180-183]

The antinociceptive activity data for compounds **152a-d** and **154a-e** are presented in Table 10. The test results indicate that these dihydropyridine analogs were less active than the parent pyridine compounds **150b** and **c**. The most potent 1,6-dihydropyridine analog **152d** exhibited less than 50 % the analgesic activity (36.0 ± 8.9 % inhibition at 25 mg/kg sc) of the parent pyridine analog **150b**, which exhibited 73 ± 11.0 % inhibition at the same dose ($p = 0.05$). The most active 1,2-dihydropyridine analog **154d** also exhibited 50 % of the potency of the parent pyridine analog **150c**, since 25 mg/kg sc of **154d** (68.8 ± 5.5 % inhibition) was equiactive ($p = 0.5$) with 12.5 mg/kg sc of **150c** (72.4 ± 3.3 % inhibition). These results suggest that reduction of the pyridine ring of compounds **150b** and **150c** to the 1,6- or 1,2-dihydropyridine analogs **152** and **154**, respectively, decreases analgesic activity. A similar decrease in activity resulting from elaboration of the pyridine to dihydropyridine analogs has been reported for a class of histamine H_2-receptor antagonists.[305] The test results also indicated that a *t*-butyl substituent at the C-6' or C-2' position of compounds **152** and **154**, respectively was the most preferential substituent for analgesic activity relative to a C-6' or C-2' methyl, *n*-butyl or phenyl substituent ($p = 0.05$). All of the dihydropyridine compounds , except compound **154a** which is not chiral, were tested as racemates.

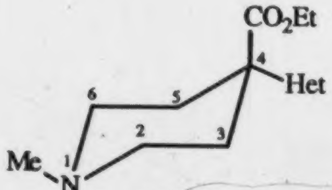
3.3.3.0.0.0. Analgesic Activity of 1-Methyl-4-propionyl-4-(pyridyl)piperidines (160a-c)

The test results summarized in Table 26 show that the 2- (**160a**), 3- (**160b**) and 4-pyridyl (**160c**) isomers exhibited 25, 50 and 50 % the analgesic activity of meperidine, respectively ($p = 0.05$). Ketobemidone (**11b**) a clinically used analog of compounds **160** is reported to be 10 times more potent than meperidine.[67] The fact that compounds **160** were less active than meperidine indicates that replacement of the 4-(*m*-hydroxyphenyl) substituent of ketobemidone by a 2-, 3- or 4-pyridyl substituent reduces analgesic activity. The absence of the *meta*-phenolic OH group in compounds **160** may partly account for their lower analgesic activity relative to meperidine. The replacement of the phenolic OH substituent present in ketobemidone by a hydrogen atom results in a compound which exhibits only 50 % the analgesic activity of meperidine.[6] A *meta*-OH group on the piperidine C-4 phenyl ring is reported to increase analgesic activity relative to the parent C-4 phenyl analog in "rigid" opioid analgesics such as the morphine, morphinan and benzomorphan classes and the "flexible" 4-carbalkoxy-4-phenylpiperidine class of opioid analgesics represented by meperidine.[5] Thus the 4-(*m*-hydroxyphenyl) compound bemidone (**11d**) is 1.5 times more potent than meperidine (**11a**), which has no phenolic OH substituent on the 4-phenyl ring.[375] In contrast to the 4-carbalkoxy-4-phenylpiperidine analgesics (ester series) a phenolic OH group on the C-4 phenyl ring present in 4-alkoxycarbonyl-4-phenylpiperidine opioid analgesics (reversed ester series) reduces analgesic activity relative to the phenyl compound.[5]

Table 26: Analgesic Activity Data for 1-Methyl-4-propionyl-4-(pyridyl)piperidines (**160a-c**) and 4-Ethoxycarbonyl-1-methyl-4-(pyridyl)piperidines (**164a-c**).


COEt
4
Het
6
5
2
3
Me
1
N

160


CO2Et
4
Het
6
5
2
3
Me
1
N

164

Entry	Het	Analgesic Activity[a], ED_{50}[b], mg/kg sc
160a	2-pyridyl	2.6 (1.4-4.62)
160b	3-pyridyl	1.4 (0.72-2.72)
160c	4-pyridyl	1.6 (0.79-3.29)
164a	2-pyridyl	2.9 (0.84-9.96)
164b	3-pyridyl	1.2 (0.69-2.1)
164c	4-pyridyl	1.9 (1.02-3.53)

Meperidine	0.6 (0.33-1.08)

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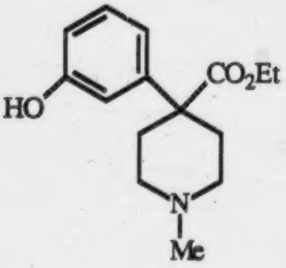
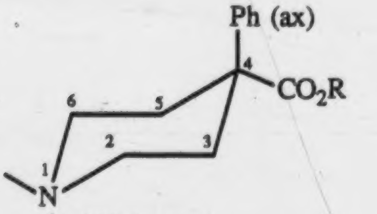
[a] 4 % NaCl-induced writhing test in rats.

[b] Numbers in brackets are the 95% confidence limits .

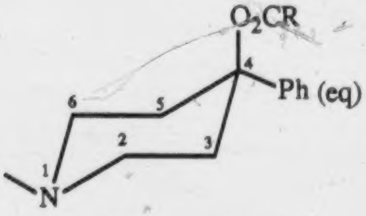


11d

This opposite effect on analgesic activity, by the presence of a phenolic OH group in the related 4-phenylpiperidine esters and reversed esters is thought to be due to the possibility of the esters adopting an axial 4-phenyl conformation (**183**, similar to the "rigid" opioids)[113] in binding with opioid receptors, whereas the reversed esters adopt an equatorial 4-phenyl conformation (**184**) in binding.[5]



183 (esters)



184 (reversed esters)

Other possible reasons for the reduction in analgesic activity of compounds **160a-c** relative to meperidine are discussed in section **3.3.5.0.0.0.** At 2 mg/kg sc the following analgesic activity (Table 27) profiles were observed among the isomeric pyridinyl ketones **160a-c**: 3-pyridyl (**160b**, 63.4 ± 5.7 % inhibition) > 2-pyridinyl (**160a**, 41.7 ± 5.3 % inhibition), $p = 0.05$; 3-pyridyl (**160b**, 63.4 ± 5.7 % inhibition) = 4-pyridyl (**160c**, 56.2 ± 6.3 % inhibition), $p = 0.5$; 4-pyridyl (**160c**, 56.2 ± 6.3 % inhibition) > 2-pyridyl (**160a**, 41.7 ± 5.3 % inhibition), $p = 0.1$. The relative order of activity among these isomeric pyridinyl compounds was therefore, 3-pyridyl = 4-pyridyl > 2-pyridyl. At 2 mg/kg sc meperidine exhibited 100 % inhibition in this test.

3.3.4.0.0.0. Analgesic Activity for 4-Ethoxycarbonyl-1-methyl-4-(pyridyl)piperidines (164a-c).

Compounds **164a-c** are the first 4-(pyridyl)-4-carbalkoxy (ester series) analogs of meperidine prepared to my knowledge. The test results summarized in Table 26 show that the 3-pyridyl (**164b**) and 4-pyridyl (**164c**) compounds exhibited similar analgesic activities, giving ED_{50}'s of 1.2 mg/kg sc and 1.9 mg/kg sc, respectively. This activity was 50 % that exhibited by meperidine (ED_{50} = 0.6 mg/kg sc). The 2-pyridyl analog **164a** was less active (ED_{50} = 2.9 mg/kg sc) than the 3- and 4-pyridyl isomers **164b** and **164c**, respectively. At 2 mg/kg sc the following relative activities (Table 27) were observed among the isomeric pyridyl esters **164a-c**: 3-pyridyl (**164b**, 60.9 ± 6.7 % inhibition) > 2-pyridyl (**164a**, 31.6 ± 4.3 % inhibition), p = 0.05; 3-pyridyl (**164b**, 60.9 ± 6.7 % inhibition) = 4-pyridyl (**164c**, 52.6 ± 5.9 % inhibition), p = 0.5, and 4-pyridyl (**164c**, 52.6 ± 5.9 % inhibition) > 2-pyridyl (**164a**, 31.6 ± 4.0 % inhibition), p = 0.1. This activity profile, 3-pyridyl = 4-pyridyl > 2-pyridyl is similar to that which was observed among the isomeric ketones (**160a-c**). The effect which the position of the pyridine ring nitrogen has upon analgesic activity is similar in both the ketone (**160a-c**) and ester (**164a-c**) series. There appears to be no distinction between the 4-propionyl and 4-ethoxycarbonyl groups with regard to the analgesic activity of compounds **160a-c** and **164a-c**. It may therefore be concluded that a C-4 propionyl substituent enhances analgesic activity relative to a C-4 ethoxycarbonyl substituent, in the presence of a C-4-(3-hydroxyphenyl) substituent, but not in the presence of a 4-(pyridyl) substituent.

The lower analgesic activity exhibited by the pyridinyl analogs **160a-c** and **164a-c** relative to meperidine could arise from a decrease in lipophilicity, resulting from the replacement of the 4-phenyl substituent by the more polar 4-(pyridyl) substituent.[301] One explanation that was given for the lower activity of a 4-(2-pyridyl) isostere of prodine (**11c**) was that solvation of the heteroatom (nitrogen) increases the size of the heteroaromatic ring causing a decrease in affinity for opioid receptors.[306] The decrease in analgesic activity of **160a-c** and **164a-c** relative to meperidine could also be due, at least in part, to a lower pKa for compounds **160** and **164** resulting from the higher electron-withdrawing effect (-I) of the pyridyl ring relative to a phenyl ring. It has been reported that electron-withdrawing (-I) substituents at the C-4 position of N-methylpiperidine decreases pKa.[376] In this regard the 2-pyridyl isomers (**160a** and **164a**) should have the lowest pKa values since the 2-pyridyl ring has the highest electron-withdrawing (-I) effect among isomeric pyridyl substituents. This is possibly reflected in the lower analgesic activity of the 2-pyridyl compounds **160a** and **164a** relative to their respective 3- and 4-pyridyl isomers. High pKa values in the 7-9 range, are required to provide extensive ionization (protonation) at physiological pH, for most opioid analgesics.[5] Determination of the pKa's for compounds **160** and **164** could be undertaken to investigate whether there is a correlation between pKa and their analgesic activity.

The Rf values for compounds **160a-c** and **164a-c** indicate that there is a bigger difference between the lipophilicities of the 2-pyridyl compounds relative to the 3- or 4-pyridyl isomers, whereas the 3- and 4-pyridinyl isomers have similar lipophilicities. The Rf values for compounds **164a, b** and **c** are 0.38, 0.33 and 0.31, respectively (Table 15). These values indicate that the 2-pyridyl isomer **164a** was the least polar and therefore should have the highest lipophilicity relative to the 3- (**164b**) and 4-pyridyl (**164c**) isomers. Compounds **164b** and **164c** had similar lipophilicities since their Rf values were relatively close. The Rf values and for that matter the lipophilicities of the isomeric pyridinyl compounds **160a-c** 0.38, 0.34 and 0.35, respectively follow a similar trend as observed for compounds **164a-c**. A correlation between lipophilicity and analgesic activity of compounds **160a-c** and **164a-c** appears to exist. An increase in lipophilicity corresponds to a decrease in analgesic activity in these pyridyl analogs of ketobemidone (ketones **160**) and meperidine (esters **164**). The determination of octanol/water partition coefficients for compounds **160** and **164** will provide further insight into the relationship between lipophilicity and analgesic activity of these compounds.

3.3.5.0.0.0. Analgesic Activity for 1,3-Dimethyl-4-propionyl-4-(pyridyl)piperidines (160d-h) and 1,3(1,2)-Dimethyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (164d, g, h, j, k, l, n)

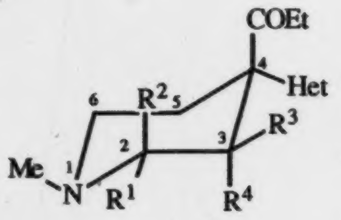
The analgesic activities exhibited by diastereoisomeric 3-methyl analogs of meperidine has been investigated by Casy *et al.*[352] These investigators showed that the *cis-* and *trans-* diastereoisomers were 11 and 1.3 times more potent, respectively, than the parent compound meperidine. It was therefore of interest to determine the effect which a 3-methyl substituent has upon analgesic activity for the new pyridinyl ketones **160a-c** and esters **164a-c**.

The analgesic test results presented in Table 27 indicate that 3-methyl-4-(pyridyl)piperidine ketones **160d-h** were generally more active than the corresponding 3-unsubstituted ketones (**160a-c**) at a dose of 2 mg/kg sc as shown by the following relative activities: **160d** > **160a** ($p = 0.01$); **160e** > **160a** ($p = 0.01$); **160g** > **160b** ($p = 0.05$). The relative potency order for the isomeric *cis*-3-methyl-4-(pyridyl)piperidine ketone analogs (**160d, f, h**) was, 2-pyridyl > 4-pyridyl > 3-pyridyl. The analgesic test results also indicate that the *cis*-3-methyl isomers in both the ketone (**160**) and ester (**164**) series were generally more active than their *trans*- 3-methyl stereoisomers as shown by the following: **160d** > **160e** ($p = 0.05$); **160f** > **160g** ($p = 0.05$); **164g** > **164h** ($p = 0.01$); **164k** > **164l** ($p = 0.01$). This is consistent with the observation that in the 4-phenylpiperidine ester series of opioid analgesics *cis*-3-methyl diastereoisomers are generally more active than their corresponding *trans*-3-methyl diastereoisomers.[5]

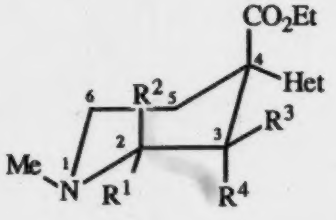
Another significant observation was that the 3-methyl substituted ketones (**160**) were generally more active than their corresponding 3-methyl substituted esters (**164**), as shown by the following: **160d** > **164d** ($p = 0.05$); **160f** > **164g** ($p = 0.05$); **160g** > **164h** ($p = 0.01$). This is in contrast to the 3-desmethyl ketones (**160a-c**), which were equipotent with their corresponding 3-desmethyl ester analogs (**164a-c**). These observations suggest that introduction of a 3-methyl substituent is more advantageous for the ketones **160a-c** than the esters **164a-c**, in terms of analgesic activity. It can also be concluded that in the 3-methyl substituted series (**160d-h** and **164d, g, h, k, l**), a 4-propionyl substituent enhances analgesic activity relative to a 4-ethoxycarbonyl substituent. This is in agreement with the relative analgesic activities observed for ketobemidone (**11b**) and bemidone (**11d**). Ketobemidone which has a 4-propionyl substituent is more active (10 times) than bemidone which differs from the former compound by having a C-4 ethoxycarbonyl substituent in place of the 4-propionyl substituent.

The *trans*-2-methyl-4-(3-pyridyl)piperidine ester **164j**, was more active than both the *cis*- (**164g**) and *trans*-3-methyl-4-(3-pyridyl)piperidine (**164h**) esters ($p = 0.05$). The higher activity of compound **164j** relative to **164g** may be governed, to a large extent, by the differences in both regio- and stereochemistry. The *trans*-2-methyl-4-(3-pyridinyl)piperidine ester **164j** has an axial 4-(3-pyridyl) orientation whereas the *cis*-3-methyl-4-(3-pyridinyl)piperidine ester **164g** has an equatorial 4-(3-pyridinyl) orientation (Fig.13). Casy and McErlane[362] have reported that in propionate esters represented by compound **185a** introduction of a 2-methyl substituent into the piperidine ring had an adverse effect upon analgesic activity that was independent of the stereochemistry of the 3-methyl substituent. However, in the acetates **185b**, introduction of a *trans*-2-methyl substituent increased analgesic activity relative to a *cis*-2-methyl substituent.

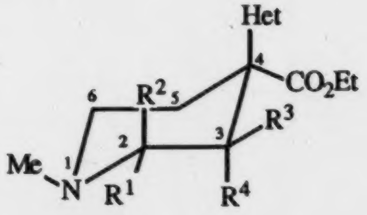
Table 27: Analgesic Activity Data for 1,3-Dimethyl-4-propionyl-4-(pyridyl)piperidines (**160a-h**) and, 1, 3-Dimethyl-4- ethoxycarbonyl-4-(pyridyl)piperidines (**164a-d, g, h, k, l**) and 1,2-Dimethyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (**164 j, n**).



160



164a-d, g, h, k, l.



164j, n.

Entry	R^1	R^2	R^3	R^4	Het	Analgesic activity, % Inhibition[a]
160a	H	H	H	H	2-pyridyl	41.7 ± 5.3
160b	H	H	H	H	3-pyridyl	63.4 ± 5.7
160c	H	H	H	H	4-pyridyl	56.2 ± 6.3
160d	H	H	H	Me	2-pyridyl	81.8 ± 2.9
160e	H	H	Me	H	2-pyridyl	70.2 ± 3.9
160f	H	H	H	Me	3-pyridyl	67.8 ± 5.0
160g	H	H	Me	H	3-pyridyl	42.4 ± 5.3
160h	H	H	H	Me	4-pyridyl	77.2 ± 4.4

164a	H	H	H	H	2-pyridyl	31.6 ± 4.0
164b	H	H	H	H	3-pyridyl	60.9 ± 6.7
164c	H	H	H	H	4-pyridyl	52.6 ± 5.9
164d	H	H	H	Me	2-pyridyl	48.7 ± 4.3
164g	H	H	H	Me	3-pyridyl	48.0 ± 5.5
164h	H	H	Me	H	3-pyridyl	19.4 ± 3.7
164j	Me	H	H	Me	3-pyridyl	66.6 ± 3.1
164k	H	H	H	Me	4-pyridyl	65.6 ± 5.1
164l	H	H	Me	H	4-pyridyl	15.4 ± 4.6
164n	Me	H	H	H	4-pyridyl	59.0 ± 4.3
Meperidine						0.6 (0.33-1.08)[b]

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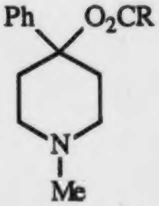
[a] 4 % NaCl-induced writhing assay in rats. Result is the mean ± SEM for five animals at a dose of 2mg/kg sc.

[b] ED_{50}, mg/kg sc. Numbers in brackets are the 95% confidence limits.

The preferred conformation of the *cis*-2-methyl substituted compound **185a** was thought to possess an equatorial 4-phenyl substituent, whereas the preferred conformation of the *trans*-2-methyl substituted compound **185a** possesses an axial 4-phenyl substituent (compare conformation of *trans*-2-methyl isomers, Fig. 13). It has also been reported that for 3-methyl and 2,5-dimethyl analogs of **185**, the highest analgesic potencies were observed for isomers in which the geometry of substitution led to a departure from 4-equatorial phenyl piperidine chairs.[362]



a, R = Me

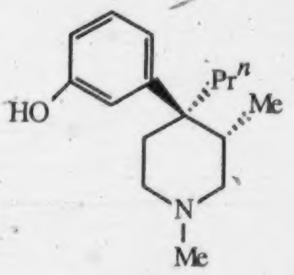
b, R = Et

185

The higher activity of **164j** relative to **164g** and **164h** may therefore be due to the fact that **164j** has an apparent solution conformation in which the C-4 pyridyl substituent is axial, whereas compounds **164g** and **164h** have preferred solution conformations in which the C-4 pyridyl substituent is equatorial. The *trans*-2-methyl-4-(4-pyridinyl)piperidine ester **164n**, which is the corresponding 4-pyridyl isomer of **164j** was more active than the *trans*-3-methyl-4-(4-pyridyl)piperidine ester **164l** ($p = 0.01$), but was equipotent with the *cis*-3-methyl-4-(4-pyridyl)piperidine ester **164k** ($p = 0.5$).

The *trans*-3-methyl-4-(2-pyridyl)piperidine ester **164e**, *trans*-2-methyl-4-(2-pyridyl)piperidine ester **164f** and the *cis*-2-methyl-4-(3- (or 4)-pyridinyl)piperidine esters **164i** and **164m** could not be separated and were not tested for analgesic activity. The 1,3-dimethyl-4-(pyridyl)piperidine ketones (**160d-h**) and 1,3- or 1,2-dimethyl-4-(pyridyl)piperidine esters (**164d, g, h, j, k, l** and **n**) were tested as racemates.

Separation and analgesic testing of the pure enantiomers will be necessary to determine whether or not there is enantioselectivity with regard to the analgesic activity of these compounds (**160d-h** and **164d, g, h, j, k, l, n**). The dextrorotatory (+) enantiomer of the related compound picenadol (**186**), is an opioid μ-receptor agonist, whereas the levorotatory (-) enantiomer is an opioid μ-receptor antagonist.[377]

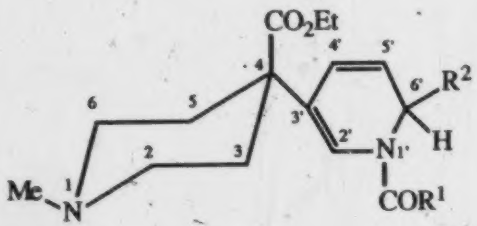


186 (picenadol)

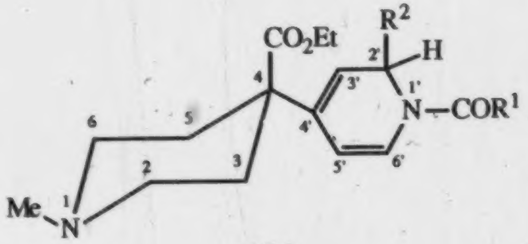
3.3.6.0.0.0. Analgesic Activities for 1-Methyl-4-ethoxycarbonyl-4-(1-acyl 1,6(1,2)-dihydropyridyl)piperidines (169c-f and 171a-m)

The test results presented in Table 28 indicate that the 1,6- and 1,2- dihydropyridyl compounds **169c-f** and **171a-m**, which are analogs of the pyridine compounds **164b** and **164c** respectively, exhibited lower analgesic activity relative to the corresponding pyridine analogs. The most potent dihydropyridine compound (**171c**, R^1 = OPh, R^2 = *n*-Bu) exhibited 69.6 ± 8.4 % inhibition at 8 mg/kg sc. The parent pyridine analog **164c** exhibited 88.2 ± 7.5 % inhibition at lower dose of 4 mg/kg sc. Therefore the most potent dihydropyridine analog exhibited half the analgesic activity of the parent pyridine analog. Replacement of an aromatic ring by substituents with extended conjugation has also been reported to result in retention of analgesic activity for the oripavine [27] (see compound **6**) and the prodine (reversed ester)[6] classes of opioid analgesics. There was no consistent structure-activity correlations in terms of R^1 and R^2 substituents. However, in the 1,6-

Table 28: Analgesic Activity Data for 1-Methyl-4-ethoxycarbonyl-4-(1,6- (or 1,2)-dihydro-1-acylpyridinyl)piperidines (**169c-f** and **171a-m**).


CO2Et
4
4'
5'
6'
R2
6
5
3'
2'
H
2
3
N1'
Me
1
N
COR1

169


R2
CO2Et
2'
H
3'
1'
4
N—COR1
6
5
4'
2
3
5'
6'
Me
1
N

171

Entry	R^1	R^2	Analgesic Activity[a], % Inhibition
169c	OMe	Ph	30.6 ± 5.8
169d	Me	Ph	inactive
169e	OPh	Ph	41.0 ± 6.4
169f	Ph	Ph	19.0 ± 6.0
171a	OPh	H	17.2 ± 5.1
171b	OPh	Me	24.2 ± 6.5
171c	OPh	*n*-Bu	69.6 ± 8.4
171d	OPh	Ph	27.0 ± 12.4

171e	OMe	Me	40.7 ± 8.9
171f	OMe	*n*-Bu	33.6 ± 5.3
171g	OMe	Ph	18.0 ± 2.8
171h	Ph	Me	34.7 ± 4.8
171i	Ph	*n*-Bu	37.4 ± 6.1
171j	Ph	Ph	45.2 ± 5.1
171k	Me	Me	59.8 ± 4.9
171l	Me	*n*-Bu	32.4 ± 7.3
171m	Me	Ph	28.0 ± 5.6
Meperidine			0.6 (0.33-1.08)[b]

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[a] 4 % NaCl-induced writhing assay in rats. Result is the mean ± SEM for five animals at a dose of 8 mg/kg sc.

[b] ED_{50}, mg/kg sc. Numbers in brackets are the 95% confidence limits.

dihydropyridine series **169c-f**, where R^2 = Ph, the carbamates were more active than the corresponding amides as shown by the following: **169c** (R^1 = OMe) > **169d** (R^1 = Me) ; **169e** (R^1 = OPh) > **169f** (R^1 = Ph) , p = 0.05. There was no significant difference between R^1 OMe and OPh substituents in terms of analgesic activity (p = 0.5). In the 1,2-dihydropyridine series **171a-d**, when R^1 = OPh, a R^2 *n*-Bu substituent (**171c**) enhanced analgesic activity relative to R^2 H (4 times), Me (2.8 times) or Ph (2.5 times) substituent (p = 0.01). A R^2 Me substituent was advantageous over a R^2 *n*--Bu or Ph substituent in terms of analgesic activity among compounds **171k-m**, where R^1 = Me (p = 0.05).

The acquisition of *in vitro* opioid receptor binding constants for compounds **164**, **169** and **171** would provide more insight into the bioisosteric relationship between the pyridine and the dihydropyridine ring systems for compounds **164**, **169** and **171**.

3.3.7.0.0.0. Analgesic Activities of 1-[2-(Pyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidines (179a-c) and 1-[2-(1-Phenoxycarbonyl-1,6(1,2)-dihydropyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidines (180 and 181a-d)

The pyridyl compounds (**179a-c**) exhibited potent analgesic activity (Table 29). The 2-pyridyl compound (**179a**) exhibited 1.3 times the analgesic potency of fentanyl at 0.002 mg/kg sc (p = 0.05). The 3-pyridyl compound (**179b**) was equipotent with fentanyl at this dose (0.002 mg/kg sc, p = 0.5), whereas the 4-pyridyl isomer (**179c**) exhibited only 10 % the activity of fentanyl, since its activity at 0.02 mg/kg sc (62.4 ± 3.9 % inhibition) was not different from that of fentanyl (54 2± 3.6 % inhibition) at 0.002 mg/kg sc at the 95 % confidence level. The higher activity of compound **179a** relative to fentanyl in this study is in contrast to the results of Zhu and co-workers who have reported[313] that compound **179a** exhibited 30 % the analgesic activity of fentanyl in the mouse hot plate test. Chagngying and Lemin have also reported that 3-methylfentanyl analogs possessing 1-[2-(pyridyl)-2-hydroxyethyl] substituents were at least 10 times less potent than the corresponding 1-[2-phenyl-2-hydroxyethyl] analog.[314] However Elpern *et al* have reported that replacement of the phenethyl substituent present in 1-phenethyl normeperidine by a β-2-pyridylethyl or a β-4-pyridylethyl substituent enhanced analgesic activity 2 and 4 times, respectively, relative to 1-phenethyl normeperidine.[308] It has also been reported that replacement of the phenyl ring of the *N*-phenethyl moiety in some morphinan opioid analgesics by a 2-pyridyl ring enhanced analgesic activity eleven times, whereas a 4-pyridyl ring reduced analgesic activity by half.[41] The observed relative activity profile for the isomeric pyridyl compounds **179a-c** was 2-pyridyl > 3-pyridyl > 4-pyridyl.

The dihydropyridine derivatives **180** and **181a-d** exhibited a lower analgesic activities than the parent pyridine compounds (Table 30). Compound **180** exhibited 58.4 ± 5.3 % inhibition at 0.4 mg/kg sc as compared to 81.0 ± 7.8 % inhibition exhibited by the parent pyridine analog **179b** at 0.02 mg/kg sc. The most active of the 1,2-dihydropyridine analogs **181d** exhibited 51.9 ± 5.6 % at 0.4 mg/kg sc relative to 89.4 ± 6.8 % inhibition exhibited by the parent pyridyl analog **179c** at 0.2 mg/kg sc. Among compounds **181a-d** a C-2' Ph substituent enhanced analgesic activity relative to the C-2' H ($p = 0.05$) or C-2' *n*-Bu ($p = 0.01$) compound. The difference in the activities of **181b** and **181d** was not significant at the 95 % confidence level.

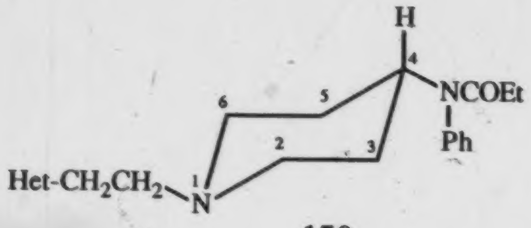
3.3.7.1.0.0. Toxicity differences between pyridines 179a-c and dihydropyridine analogs 180 and 181a-d.

Administration of compounds **179a-c** at a dose of 4 mg/kg sc induced muscle rigidity in rats.The most potent analgesic agent of this group of pyridine compounds (**179a-c**), **179a** (Het = 2-pyridyl) was lethal to 2 out of 5 rats. The 3-pyridinyl isomer was (**179b**, Het = 3-pyridyl) was lethal to 1 out of 5 rats, whereas the 4-pyridyl isomer did not cause death to any of the 5 rats to which it was administered at 4 mg/kg sc. This toxicity profile, 2-pyridyl > 3-pyridyl > 4-pyridyl, parallels the analgesic activity profile of compounds **179a-c** which is 2-pyridyl > 3-pyridyl > 4-pyridyl. The onset of rigidity was

10-15 minutes following administration of the test compound. Rigidity lasted 2-2.5 hr for animals that recovered. Animals that did not recover died 3-4 hr after administration of the test compound. A similar muscle rigidity in animals used to screen a series of fentanyl analogs has been reported.[80]

In contrast to the pyridine compounds **179a-c**, the dihydropyridine analogs, **180** and **181a-d**, did not induce muscle rigidity at a dose of 4 mg/kg sc. Compound **181a** did not induce muscle rigidity even at a dose of 40 mg/kg sc. This dramatic reduction in toxicity for the dihydropyridine compounds (**180** and **181a-d**) relative to the pyridyl analogs is an important lead which may provide a method to improve the therapeutic index of drugs possessing a pyridine ring.

Table 29: Analgesic Activity Data for 1-[2-(Pyridyl)ethyl]-4-(N-phenyl-N-propionyl)amino]piperidines (**179a-c**)



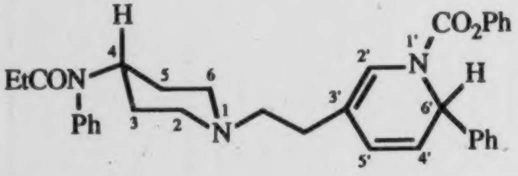
179

Entry	Het	Analgesic Activity[a] ,ED_{50}[b],mg/kg sc
179a	2-pyridyl	2.3×10^{-4} (2.0×10^{-5} -3.0×10^{-3})
179b	3-pyridyl	8.5×10^{-4} (4.4×10^{-5} -3.0×10^{-2})
179c	4-pyridyl	8.7×10^{-3} (2.0×10^{-3} -3.0×10^{-2})
Fentanyl		2.1×10^{-3} (2.0×10^{-4} -3.0×10^{-3})

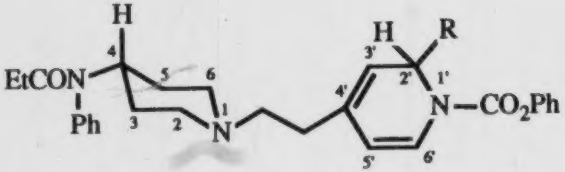
[a] 4% NaCl-induced writhing test in rats.

[b] Numbers in brackets are the 95% confidence limits .

Table 30: Analgesic Activity Data for 1-[2-(1,6- or 1,2-Dihydro-1-phenoxycarbonylpyridinyl)ethyl]-4-(N-phenyl-N-propionyl)amino]piperidines (**180** and **181a-d**).



180



181

Entry	R	Analgesic Activity[a], % Inhibition
180	Ph	58.4 ± 6.0
181a	H	33.7 ± 3.8
181b	Me	35.9 ± 8.2
181c	*n*-Bu	18.1 ± 8.7
181d	Ph	51.9 ± 5.6

Fentanyl	2.1×10^{-3} (2.0×10^{-4} - 3.0×10^{-3})[b]

[a] 4 % NaCl-induced writhing assay in rats. Result is the mean ± SEM for five animals at a dose of 0.4 mg/kg sc.

[b] ED_{50}, mg/kg sc. Values in brackets are the 95% confidence limits.

3.3.8.0.0. Summary of Structure-Activity Relationships

3.3.8.1.0. Structure-activity correlations for aryloxysulfonamides (134, 143 and 144)

Among the tetrahydropyridylidene- or piperidylidene-2-aryloxysulfonamide series of compounds (**134**, **143** and **144** , Table 6) the following general analgesic activity profiles were observed:

1) Piperidines > 1,2,5,6-tetrahydropyridines > 1,2,3,6-tetrahydropyridines.

2) R^2 = Me, *n*-Bu or Ph > R^2 = H.

3.3.8.2.0. Structure-activity correlations for 1-methylpiperidylidene-2-(pyridine)sulfonamides and dihydropyridine analogs

Among the isomeric pyridinyl compounds **150** and dihydropyridinyl analogs **169,171**, analgesic activity profiles were as follows:

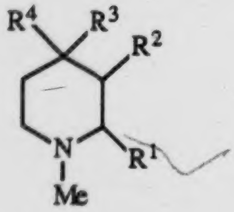
1) 2-Pyridyl = 4-pyridyl > 3-pyridyl.

2) Pyridines > dihydropyridines.

3) R = *t*-Bu > R = H, Me, *n*-Bu, or Ph.

3.3.8.3.0. Structure-activity correlations for 1-methyl-4-(pyridyl)piperidines and 4-(1,2 or 1,6-dihydropyridine) analogs

The following analgesic activity profiles were observed for the ketobemidone and meperidine analogs represented by structure **187**.



187

1) When $R^1 = R^2 = H$, and R^3 = pyridyl; then R^4 COEt is equipotent with R^4 CO_2Et.

2) When $R^1 = H$, R^2 = Me and R^3 = pyridyl; then R^4 COEt > R^4 CO_2Et.

3) When $R^1 = H$, R^2 = Me, R^3 = pyridyl and R^4 = COEt or CO_2Et; then *cis*-(3-Me/pyridyl) > *trans*-(3-Me/pyridyl).

4) When $R^1 = H$, R^3 = pyridyl, and R^4 = COEt; then R^2 Me > R^2 H.

5) When $R^1 = H$, R^2 = Me *cis*-(3-Me/pyridyl) and R^4 = COEt; then R^3 2-pyridyl > R^3 3-pyridyl = R^3 4-pyridyl.

6) When $R^1 = H$, R^2 = Me *trans*-(3-Me/pyridyl) and R^4 = COEt; then R^3 2-pyridyl > R^3 3-pyridyl.

7) When $R^1 = H$, R^2 = Me *cis*-(3-Me/Pyridyl) and R^4 = CO_2Et; then R^3 4-pyridyl > R^3 3-pyridyl is equipotent with R^3 2-pyridyl.

8) When $R^1 = H$, R^2 = Me *trans*-(3-Me/pyridyl) and R^4 = CO_2Et; then R^3 3-pyridyl is equipotent with R^3 4-pyridyl.

9) When R^1 = Me *trans*-(2-Me/Pyridyl) , R^2 = H and R^4 = CO_2Et; then R^3 3-pyridyl is equipotent with R^3 4-pyridyl.

10) When $R^1 = R^2 = H$ and R^4 = COEt or CO_2Et; then R^3 3-pyridyl = R^3 4-pyridyl > R^3 2-pyridyl.

11) When R^3 = pyridyl and R^4 = CO_2Et; then R^1 Me *trans*-(2-Me/pyridyl) > R^2 Me *trans*-(3-Me/Pyridyl).

12) When $R^1 = R^2 = H$ and $R^4 = CO_2Et$; then R^3 3-pyridyl or 4-pyridyl > R^3 1,6- or 1,2-dihydropyridine system.

3.3.8.4.0.0. Structure-activity correlations for 1-[2-(Pyridyl)ethyl]-4-[(N-phenyl-N-propionyl)amino]piperidines and 1-[2-(1,2 or 1,6-dihydropyridine)ethyl] analogs

For the fentanyl analogs represented by structures **179** (Table 22), **180** and **181** (Table 24), the following general structure-activity profiles were observed:

1) 2-pyridyl > 3-pyridyl > 4-pyridyl.

2) 3- or 4-pyridyl > 1,6- or 1,2-dihydropyridyl.

4.0.0.0.0.0. EXPERIMENTAL

4.1.0.0.0.0. PHYSICAL CONSTANTS AND SPECTROSCOPY

Melting points were determined with a Thomas Hoover apparatus and are uncorrected. Infrared (IR) spectra were taken on a Nicolet 5DX or Perkin-Elmer 267 spectrophotometer. High resolution nuclear magnetic resonance (NMR) spectra were recorded for solutions of the compounds in deuterochloroform ($CDCl_3$) or dimethylsulfoxide-d_6 (DMSO-d_6), with a Bruker AM-300 spectrometer. High resolution (exact) mass spectra (HRMS) were recorded with an AEI MS-50 mass spectrometer. Microanalyses were performed by the microanalytical laboratory, Department of Chemistry, University of Alberta.

4.2.0.0.0.0. CHROMATOGRAPHY

Column chromatography (CC) was performed using silica gel (Merck type 7734, 100-200 mesh), unless otherwise stated. Preparative thin layer chromatography (TLC) was performed with Camag Kieselgel DF-5 plates, 1.0 mm in thickness, activated at 105 ^{o}C for 1-2 hr prior to use. Reaction progress and purity of products were checked using Merck silica coated plastic plates, 250 µM in thickness. Spots were visualized by shortwave ultraviolet light and iodine vapor.

4.3.0.0.0.0. SOLVENTS AND REAGENTS

Tetrahydrofuran and diethyl ether were dried by distillation from sodium-benzophenone just prior to use. Methanol and ethanol were purified by distillation from magnesium. Ethyl acetate, acetonitrile, benzene and toluene were dried by distillation from calcium hydride. Pyridine and triethylamine were distilled from potassium hydroxide pellets. All organometallic reagents were purchased in "sure-sealed" containers from the Aldrich Chemical company, unless otherwise stated. N-Methyldiethanolamine, 1,4-dioxa-8-azaspiro[4.5]decane, 2- and 3-pyridyl acetonitriles, ethyl 2-and 3-pyridyl acetates, and

4-pyridylacetic acid hydrochloride, were also purchased from the Aldrich Chemical company.

4.4.0.0.0.0. SYNTHETIC CHEMISTRY

N-Unsubstituted-1,2-dihydropyridines (**131a-c**) were prepared as lithium hydroxide-free solutions in ether according to the procedure of Ondrus *et al.*.[251] 1-Methyl-1,2-dihydropyridine was prepared according to the method of Fowler.[204] Phenoxysulfonyl and 4-chlorophenyloxysulfonyl azides were prepared by the procedure of Hedayatullah and Hugueny.[378] Benzenesulfinyl azide was prepared according to the method of Maricich *et al.*.[330] 3-Pyridinesulfonyl azide was synthesized using the method of Warren.[291] The procedure of Talik and Plazek[339] was used to prepare 2- and 4-pyridinesulfonyl chlorides. 4-Pyridylacetonitrile was synthesized by the method of Betts and Davey.[379] 3-Picolyl lithium was prepared using the method of Kaiser and Petty.[368] Ethyl 4-pyridyl acetate was prepared by ethanolysis of 4-pyridylacetic acid hydrochloride

4.4.1.0.0.0. 1-Methylpyridinium Iodide (130)

Methyl iodide (7.613 g, 53.55 mmol) was added dropwise to a solution of pyridine (3.955 g, 50 mmol) in dry THF (200 ml).with stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 °C and refluxed for 10 hr. The white crystalline precipitate was filtered and washed with ether to afford **130** as a white crystalline powder (10.8 g, 98 %); m.p. 116-117 °C (decomposition).

4.4.1.1.0.0. 1-Methyl-2-substituted-1,2-dihydropyridines (131e-g)

General Procedure A

A solution of an alkyl (Me, *n*-Bu) or phenylmagnesium chloride (15 mmol) in dry THF (3 M for MeMgCl; 2 M for *n*-BuMgCl or PhMgCl) was added dropwise with stirring to a suspension of N-methylpyridinium iodide (2.27 g, 10 mmol) in anhydrous ether

(50 ml) at -78 °C under a nitrogen atmosphere. The reaction was allowed to proceed for 45 minutes at -78 °C, prior to warming to 0 °C. Distilled water (4g, 220 mmol) was added dropwise, and stirring continued for an additional 30 minutes at 0 °C. The organic layer was separated, quickly washed with water (2 x 25 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo* at 25 °C to give an oil. Purification using a short column of basic alumina (Brockman Activity Grade 1) with ether as eluent, yielded the respective products **131e-g** as viscous oils. Physical and spectral data for **131e-g** are presented in Table 2. These products were used immediately for subsequent reactions.

4.4.1.2.0.0. 1,2,3,6-Tetrahydropyridylidene-2-aryloxsulfonamides (134a-h) General Procedure B

A solution of the 1,2-dihydropyridine (**131**, 10 mmol), lithium hydroxide-free for **131a-c**, in anhydrous ether (25 ml), was added dropwise with stirring to a solution of aryloxysulfonyl azide (**132**, 10 mmol) in dry ether (25 ml) at 0 °C under a nitrogen atmosphere. The reaction was allowed to proceed at 0 °C for 45 minutes prior to warming to 25 °C. The white product that precipitated was filtered and recrystallized from ethyl acetate : hexane (1 : 5 v/v). The IR and ^{1}H NMR spectral data for products **134a-h** are summarized in Table 3, whereas their physical data are presented in Table 6.

4.4.1.2.1.0. 1-Phenylsulfinyl-2-n-butyl-1,2-dihydropyridine (139)

A solution of **131b** (1.37 g, 10 mmol) in dry ether (25 ml) was added to a solution of phenylsulfinyl azide (1.67 g, 10 mmol) in acetonitrile (20 ml) at 0 °C as described under Procedure B. The dark brown reaction mixture was placed in a refrigerator for 12 hr. The resulting crystals were filtered and recrystallized from acetonitrile : hexane (1 : 2) to give **139** (1.04 g 40 %); m.p. 81-83 °C; ^{1}H NMR ($CDCl_3$), δ: 0.9 (t, J = 7Hz, 3H, $CH_2\mathit{CH_3}$), 1.3 (m, 4H, $CH_2\mathit{CH_2CH_2}CH_3$), 1.5 (m, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 4.24 (m, 1H, H-5), 5.05 (d, J = 9.8Hz of d, J = 4Hz of d, J = 1.5Hz, 1H, H-5), 5.65 (d, J =

9.8Hz of d, J = 5Hz of d, J = 1.5Hz, 1H, H-4), 7.05 (d, J = 7Hz of d, J = 1.5Hz, 1H, H-6). Anal. calcd. for $C_{15}H_{19}NOS$: C, 68.97; H, 7.33; N, 5.36. Found: C, 68.66; H, 7.21; N, 5.43.

4.4.1.2.2.0. 1-Methyl-5-phenylsulfinyl-1,2-dihydropyridine (140)

A solution of **131d** (0.5 g, 5.2 mmol) in dry ether (15 ml) was added to a solution of phenylsulfinyl azide (0.84 g, 5 mmol) in acetonitrile (15 ml) at 0 ^{o}C as described under Procedure B. The solid which precipitated was recrystallized from ethyl acetate to afford **140** as pale yellow crystals (0.54 g 50 %); m.p. 69-71 ^{o}C; IR (KBr): 1638, 1589 cm^{-1} ; ^{1}H NMR ($CDCl_3$), δ: 2.85 (s, 3H, NMe), 4.18 (m, 2H, H-2), 5.1 (m, 1H, H-3), 5.74 (m, 1H, H-4), 6.92 (s, 1H, H-6), 7.4-7.6 (m, 5H, Ph). Exact mass, calcd. for $C_{12}H_{13}NOS$: 219.0718; found (HRMS) : 219.0717.

4.4.1.3.0.0. 1,2,5,6-Tetrahydropyridylidene-2-phenoxysulfonamides (143a-g) General Procedure C

Neutral aluminum oxide (Al_2O_3, 5 g, Brockman Activity 1) was suspended in a solution of **134** (1.0 mmol) in chloroform (25 ml), and the mixture was allowed to stir for 24 to 120 hr at 25 ^{o}C (**134a-b**, 24 hr; **134c**, 48 hr; **134d-g**, 120 hr). The mixture was filtered and the aluminium oxide was washed with methanol (2 x 25ml). The solvent from each organic solution was removed *in vacuo* and the combined oil residues were purified by silica gel TLC using ethyl acetate : hexane (2 : 1 v/v) as development solvent. With the exception of **143a** the products were obtained as mixtures along with starting material. The Rf values of the products (**143**), and Rf and % recovery of starting materials (**134**) were: **143b** (Rf 0.55), **134b** (Rf 0.6, 32 % recovery); **143c** (Rf 0.42), **134c** (Rf 0.48, 12 % recovery); **143d** (Rf 0.40), **134d** (Rf 0.45, 14 % recovery); **143e** (Rf 0.63), **134e** (Rf 0.67, 5 % recovery); **143f** (Rf 0.8), **134f** (Rf 0.87, 36 % recovery); **143g** (Rf 0.52), **134g** (Rf 0.61, 32 % recovery). The products were recrystallized from ethyl acetate : hexane (1 : 1 v/v). Spectral and physical data for compounds **143a-g** are summarized in Tables 4 and 6, respectively.

4.4.1.4.0.0. Piperidylidene-2-aryloxysulfonamides (144a-h) General Procedure D

Hydrogenation of **134a** (0.2 g, 0.75 mmol) in ethyl acetate (50 ml) using hydrogen gas at 30 psi in the presence of 10 % palladium-on-charcoal (50 mg) for 10 hr at 25 °C, followed by filtration and removal of the solvent *in vacuo* afforded **144a** (0.184g, 91%) after recrystallization from ethyl acetate : hexane (1 : 2 v/v). The spectral and physical data for **144a-h**, which were all prepared using this procedure, are presented in Tables 5 and 6, respectively.

4.4.1.4.1.0. 1-Methylpiperidylidene-2-sulfamic acid (145)

Hydrogenation of **144d** (0.15 g, 0.56 mmol) in methanol (50 ml) using hydrogen gas at 30 psi in the presence of 10 % palladium-on-charcoal (0.3 g) for 4 hr, at 25 °C, followed by filtration removal of solvent and recrystallization from ethyl acetate : hexane (2 : 1 v/v) afforded **145** as a white crystalline powder (0.09 g, 83 %); m.p. 218-220 °C; IR (KBr): 3280 (OH) and 1550 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$), δ: 1.6-1.9 (m, 4H, H-4, H-5), 3.0-3.2 (m, 5H, H-3, NMe), 3.5 (m, 2H, H-6), 10.3 (br s, 1H, OH, exchanged with deuterium oxide). Anal. calcd. for $C_6H_{12}N_2O_3S$: C, 37.45; H, 6.29; N, 14.57. Found: C, 37.45; H, 6.28; N, 14.53.

4.4.2.0.0.0. 2-Pyridinesulfonyl azide (146a)

2-Pyridinesulfonyl chloride (3.55g, 20 mmol) prepared by chlorination of 2-mercaptopyridine according to the procedure of Talik and Plazek,[339] was added to a solution of sodium azide (3.25 g, 50 mmol) in 95 % ethanol (50 ml) at 0 °C under a nitrogen atmosphere. The reaction was allowed to proceed with stirring at 0 °C for 6 hr.

Distilled water (30 ml) was added and the mixture extracted with dichloromethane (3 x 50 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed *in vacuo* at 25 ^{o}C, to afford **146a** as a colorless oil (2.46 g, 66 % yield); IR (neat): 2140 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$), δ: 7.7 (d, J = 6Hz of d, J = 8Hz, 1H, H-5), 8.08 (m, 2H, H-3, H-4), 8.85 (d, J = 6Hz, 1H, H-6). Exact mass calcd. for $C_5H_4N_4O_2S$: 184.0055; found (HRMS): 184.0050.

4.4.2.1.0.0. 4-Pyridinesulfonyl azide (146c)

4-Pyridinesulfonyl chloride (2.0 g, 11.27 mmol) in chloroform (15 ml) prepared by chlorination of 4-mercaptopyridine according to the method of Talik and Plazek[339], was added to a vigorously stirred suspension of dry sodium azide (3.25 g, 50 mmol) in dry acetonitrile (50 ml) at -20 ^{o}C under a nitrogen atmosphere. The reaction was allowed to proceed with stirring at -20 ^{o}C for 6 hr. The mixture was filtered (using a fine sintered glass filter) and the solvent was removed *in vacuo* to afford **146c** (1.5 g, 62%) as an oil which solidified on standing in a refrigerator; m.p. 54-55 ^{o}C; IR (KBr): 2155 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$), δ: 7.8 (d, J = 6Hz, 2H, pyridine H-3, H-5), 9.0 (d, J = 6Hz, 2H, pyridine H-2, H-6). Anal. calcd. for $C_5N_4O_2S$: C, 32.61; H, 2.19; N, 30.44. Found: C, 32.28; H, 2.17; N, 30.20.

4.4.2.2.0.0. 1-Methyl-1,2,3,6-tetrahydropyridylidene-2-(pyridyl)sulfonamides (148a-c)

A solution of 1-methyl-1,2-dihydropyridine (**131d**, 1.0 g, 10.5 mmol), in anhydrous ether (10 ml), was added to a solution of the pyridinesulfonyl azide, (**146 a-b**, 2.0 g, 11 mmol) in anhydrous ether (20 ml) at 0 ^{o}C, according to Procedure B. The solid product which precipitated was filtered and recrystallized from ethyl acetate : hexane (3 : 1 v/v). Compound **148c** was prepared using a modification of this procedure. The dihydropyridine solution was added dropwise with stirring to a solution of **146c** (2.0 g, 11 mmol) in dry acetonitrile (20 ml) at -20 °C under a nitrogen atmosphere. The reaction was allowed to proceed for 30 minutes at -20 °C prior to warming to 25 °C. After 2 hr the solvent was removed *in vacuo* at 40 °C and the product (**148c**, 2.1 g, 80 % yield) was recrystallized from ethyl acetate : hexane (4 : 3 v/v). The spectral and physical data for compounds **148a-c** are presented in Tables 7 and 8, respectively.

4.4.2.2.0.0. 1-Methyl-1,2,5,6-tetrahydropyridylidene-2-(pyridyl)sulfonamides (149)

Compound **148c** (0.251 g, 1 mmol) was chromatographed using a silica gel column with ethyl acetate as the eluting solvent to afford compound **149** (0.22 g, 87.6 % yield) in addition to **148c** (0.02 g, 8 % recovery). Compound **149** was recrystallized from ethyl acetate-hexane (4 : 3 v/v). The spectral and physical data for **149** are presented in Tables 7 and 8, respectively.

4.4.2.3.0.0. 1-Methylpiperidylidene-2-(pyridyl)sulfonamides (150a-c)

Compounds **148a-c** (0.251 g, 1 mmol) were hydrogenated according to Procedure D except that methanol was used in place of ethyl acetate as solvent. The products **150a-c** were recrystallized from ethyl acetate : hexane (2:1 v/v). The spectral and physical data for **150a-c** are summarized in Tables 7 and 8, respectively.

4.4.2.3.1.0. 1-Methylpiperidylidene-2-(1,6-dihydro-1-phenoxycarbonyl-6-alkyl(phenyl)-3-pyridinyl)sulfonamides (152a-d) General Procedure E

To a solution of **148b** (0.253 g, 1.0 mmol) in dry THF (20 ml) at -78 °C under a nitrogen atmosphere, phenyl chloroformate (0.19 g, 1.2 mmol) was added dropwise with stirring. The reaction was allowed to proceed for 2 hr. A solution of the appropriate alkyl or phenylmagnesium chloride (1.2 mmol) in THF (3 M for MeMgCl and *t*-BuMgCl; 2 M for *n*-BuMgCl and PhMgCl) was added slowly. The reaction was allowed to proceed at -78 °C for 30 minutes prior to warming to 0 °C. Distilled H_2O (5 ml) was added dropwise and stirring continued for 20 minutes. The organic layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The solvent from the combined organic fractions was removed *in vacuo* at 25 °C, and the viscous residue was chromographed (TLC) over silica gel using ethyl acetate as development solvent to separate the 1,6-dihydropyridine products **152a-c** from the 1,4-dihydropyridine isomers **153a-c**. The Rf values for the products were: **152a**, 0.45; **153a**, 0.56; **152b**, 0.73; **153b**, 0.8; **152c**, 0.55; **153c**, 0.60; **152d**, 0.63. The spectral and physical data for compounds **152a-d** and **153a-c** are summarized in Tables 9 and 10, respectively.

4.4.2.3.2.0. 1-Methylpiperidylidene-2-(1,2-dihydro-1-phenoxycarbonyl-4-pyridinyl)sulfonamide (154a) General Procedure F

Phenyl chlorofomate (0.19 g, 1.2 mmol) was added dropwise with stirring to a solution of **148c** (0.253 g, 1.0 mmol) in dry methanol (30 ml) at -78 °C, under a nitrogen atmosphere. The reaction was allowed to proceed for 45 minutes. Sodium borohydride ($NaBH_4$, 0.38 g, 10 mmol) was added slowly in aliquots and the reaction allowed to proceed at -78 °C for an additional 1 hr, at the end of which time the reaction mixture was poured onto crushed ice (40 g). The mixture was extracted with chloroform (3 x 40 ml). The combined chloroform extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* at 25 °C to obtain an oil-like residue which was chromatographed (TLC) over silica gel using ethyl acetate as development solvent to afford **154a** (Rf 0.6, 0.165 g, 44 %) as a viscous oil which solidified on standing in a refrigerator. The spectral and physical data for compound **154a** are presented in Tables 9 and 10, respectively.

4.4.2.3.3.0. 1-Methylpiperidylidene-2-(1,2-dihydro-2-alkyl (phenyl)-1-phenoxycarbonyl-4-pyridinyl)sulfonamides (154b-e)

Phenyl chloroformate (0.19 g, 1.2 mmol) and the appropriate alkyl or phenylmagnesium chloride (1.2 mmol) in THF(3 M solution for MeMgCl and *t*-BuMgCl; 2 M for *n*-BuMgCl or PhMgCl) were added to a solution of **148c** (0.253 g, 1.0 mmol) in THF (20 ml) according to Procedure E to afford compounds **154b-e** as the sole products. These products were purified by silica gel TLC as described for compounds **152a-d**. The Rf values of the products were: **154b**, 0.64; **154c**, 0.71; **154d**, 0.72; **154e**, 0.69. The spectral and physical data for compounds **154b-e** are presented in Tables 9 and 10, respectively.

4.4.3.0.0.0. *N*-(2-Hydroxyethyl)-*N*-(2-hydroxypropyl)methylamine

A mixture of freshly distilled N-methylethanolamine (45.0 g, 0.6 mol), freshly distilled 1-bromo-2-propanol (83.4 g, 0.6 mol) and dry triethylamine (60.71 g, 0.6 mol) were heated together at reflux in dry benzene (200 ml) for 48 hr. The reaction mixture was allowed to cool and the resulting crystalline solid was filtered off. The solvent from the filtrate was removed *in vacuo* at 40 ^{o}C and the resulting viscous liquid was distilled to afford N-(2-Hydroxyethyl)-N-(2-hydroxypropyl)methylamine (70 g, 75%); b.p. 85-88 ^{o}C/3.5 mmHg; ^{1}H NMR ($CDCl_3$), δ: 1.15 (d, J = 6Hz, 3H, $CHCH_3$), 2.3-2.67 (m, 7H, N-Me, NCH_2), 3.55 (s, 2H, OH, exchanged with deuterium oxide), 3.67 (t, J = 6Hz, 2H, CH_2CH_2OH), 3.9 (m, 1H, *CH*OH).

4.4.3.1.0.0. *N*-*bis*-(2-Chloroethyl)methylamine hydrochloride (156a) and *N*-(2-chloroethyl)-*N*-methyl-2-chloropropylamine hydrochloride (156b)

N-Methyldiethanolamine (7.745 g, 65 mmol) in chloroform (6 ml) was added to thionyl chloride (17.013 g, 143 mmol) in chloroform (8 ml) at 0 ^{o}C under a nitrogen atmosphere.[353] The reaction mixture was allowed to warm up to 25 °C prior to heating at reflux for 2 hr. The reaction mixture was chilled in a refrigerator and the white crystalline salt was filtered, washed with ether (3 x 150 ml) and dried *in vacuo* at 25 °C to afford **156a** (9.1 g, 72.8 %); m.p. 108-110 °C.

A similar procedure, employing *N*-(2-hydroxyethyl)-*N*-(2-hydroxypropyl)methylamine in place of *N*-methyldiethanolamine, was used to synthesize *N*-(2-chloroethyl)-*N*-(2-chloropropyl)methylamine hydrochloride **156b**, which was recrystallized from hot acetone (76 % yield); m.p. 117-118 °C (literature value 112-113 °C).[352]

4.4.3.2.0.0. 1-Methyl-4-cyano-4-(pyridyl)piperidines (158a-c) General Procedure G

N-Methyl-*N*-bis-(2-chloroethyl)amine hydrochloride (**156a**, 4.04 g, 20 mmol), the appropriate distilled 2-, 3- or 4-pyridylacetonitrile (**157**, 2.36 g, 20 mmol), hexadecyltri-*n*-butylammonium bromide (0.51 g, 1 mmol) and freshly prepared 70 % v/w aqueous sodium hydroxide (20 ml) were stirred together vigorously at 100 °C for 30 minutes, according to a similar procedure used by Cammack and Reeves.[353] The reaction mixture was poured onto distilled water (100 ml), cooled to 25 °C, and extracted with ether (3 x 100 ml). The combined ether extracts were extracted with 10 % hydrochloric acid (2 x 100 ml). The aqueous extract was basified with 20 % sodium hydroxide and extracted with ether (3 x 100 ml). The combined ether extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* at 40 °C. The gummy product obtained was recrystallized from hot hexane. The chemical yields, physical and microanalytical data for **158a-c** are presented in Table 11, whereas the spectral data are summarized in Table 12.

4.4.3.3.0.0. 1,3-Dimethyl-4-cyano-4-(pyridyl)piperidines (158d-h)

N-(2-Chloroethyl)-*N*-(2-chloropropyl)methylamine hydrochloride (**156b**, R = CH_3, 4.13 g, 20 mmol), the appropriate distilled pyridylacetonitrile (**153**, 2.36 g, 20 mmol), hexadecyltri-*n*-butylammonium bromide (0.51 g, 1 mmol) and freshly prepared 70% w/v aqueous sodium hydroxide (20 ml) were stirred together vigorously according to Procedure G to yield compounds **158d-h**. The diastereoisomers **158e-h** were separated by silica gel TLC using chloroform : methanol (7 : 1 v/v) as development solvent. The Rf values were as follows: **158d**, 0.71; **158e**, 0.67; **158f**, 0.54; **158g**, 0.71; **158h**, 0.52. The physical and spectral data for compounds **154d-h** are summarized in Tables 11 and 12, respectively.

4.4.3.4.0.0. 1-Methyl-4-propionyl-4-(pyridyl)piperidines (160a-c)

General Procedure H

To a solution of nitrile **158a**, **b** or **c** (2.01 g, 10 mmol) in dry ether (100 ml) at 0 °C, was added with stirring, a solution of ethylmagnesium bromide (2.67 g, 20 mmol) in dry ether (10 ml) under a nitrogen atmosphere. The reaction mixture was allowed to warm up to 25 °C and stirring was continued for 24 hr. Saturated ammonium chloride solution (40 ml) was added slowly with external cooling (ice-bath). The ice-bath was removed and stirring was continued for 10 hr. The ether layer was separated and the aqueous layer was basified (20 % NaOH) and extracted with chloroform (3 x 50 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed *in vacuo* at 40 °C. The residue was purified by silica gel TLC using chloroform : methanol (1:1 v/v) as development solvent, to afford **160a-b** as oils. The Rf values for the products were: **160a**, 0.38; **160b**, 0.34. The physical data are presented in Table 13 and the IR and ^1H NMR spectral data are summarized in Table 14. A similar reaction using **158c** afforded only 10 % of **160c** as an oil (Rf 0.35) and 60 % of the descyano product **161** (Rf 0.3, m.p.51-53 °C, recrystallized from hexane); ^1H NMR ($CDCl_3$), δ: 1.7-2.4 (m, 6H, H-3ax, H-5ax, H-2ax, H-6ax, H-3eq, H-5eq), 2.4 (s, 3H, NMe), 2.6 (m, 1H, H-4), 3.03 (m, 2H, H-2eq, H-6eq), 7.2 (d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-3, H-5), 8.6 (d, J = 1.5Hz of d, J = 6Hz, 2H, pyridine H-2, H-6).

4.4.3.5.0.0. 1,3-Dimethyl-4-propionyl-4-(pyridyl)piperidines (160e-g)

The selected nitrile **158d,** e or **f** (2.15 g, 10 mmol) was reacted with ethylmagnesium bromide (25 mmol) in dry ether (100 ml) at 25 °C according to Procedure H. The imine product which was obtained after work-up with saturated ammonium chloride solution was refluxed with 10% hydrochloric acid (50 ml) for 24 hr. The reaction mixture was basified with 20 % w/v NaOH solution and extracted with chloroform (4 x 50 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* at 40 °C to obtain the target ketone **160e, f** or **g** respectively, which was purified by TLC over silica gel using chloroform : methanol (7 : 1 v/v) as the development solvent; Rf values for **160e, f** and **g,** were 0.52, 0.46 and 0.44, respectively. The physical and spectral data for **160e-g** are summarized in Tables 13 and 14, respectively.

4.4.4.0.0.0. *N-bis*-(2-Chloroethyl)methylamine (mechloretamine, 162a) and *N*-(2-Chloroethyl)-*N*-(2-chloropropyl)methylamine (162b)

N-bis-(2-Chloroethyl)methylamine hydrochloride (16.23 g, 84 mmol) was dissolved in distilled water (60 ml). The solution was basified with aqueous sodium hydroxide (60 ml, 20 % w/v) and extracted with ether (4 x 100 ml).The combined ether extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* at 30 °C. The resulting liquid was distilled to afford **162a** (10.2 g, 77.6 % yield); b.p. 63 °C/1.7 mm Hg.

N-(2-Chloroethyl)-*N*-(2-chloropropyl)methylamine (**162b**, b.p. 60 °C/2.5 mm Hg) was prepared in 94 % chemical yield by a similar procedure using *N*-(2-chloroethyl)-*N*-(2-chloropropyl)methylamine hydrochloride (**152b**); ^1H NMR ($CDCl_3$), δ: 1.57 (d, J =

6Hz, 3H, CHCH_3), 2.43.(s, 3H, NMe), 2.7 (t, J = 6Hz, 2H, CH_2CH_2Cl), 2.9 (d, J = 6Hz, 2H, $CHCH_2$), 3.6 (t, J = 6Hz, 2H, CH_2CH_2Cl), 4.1 (m, 1H, CH_2CHCH_3).

4.4.4.1.0.0. 1-Methyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (164a-c) General Procedure I

The appropriate distilled ethyl pyridyl acetate (**163**, 3.304 g, 20 mmol) and sodium hydride (1.84 g, 80 mmol, in 60 % mineral oil suspension) were heated at reflux in dry THF (200 ml) under a nitrogen atmosphere until evolution of hydrogen had stopped. Freshly distilled mechlorethamine (**162a**, R = H, 3.12 g, 20 mmol) in dry THF (15 ml) was added and heating at reflux was continued for 24 hr. The solid was filtered off and the solvent was removed from the filtrate *in vacuo*at 40 °C to give an oil-like residue, which was dissolved in ether (150 ml) and extracted with 10 % HCl (2 x 80 ml). The combined aqueous extracts were basified with sodium hydroxide (20 % w/v) and extracted with ether (4 x 100 ml). The combined ether extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* at 40 °C to afford the product. Compound **164a** was obtained as an oil and did not crystallize from hexane which was used to recrystallize **164b** and **c**. The physical and spectral data for **164a-c** are given in Tables 15 and 16, respectively. The ^{13}C NMR spectral data for **164c** are summarized in Table 17.

4.4.4.2.0.0. Dimethyl-4-ethoxycarbonyl-4-(pyridyl)piperidines (164 d-n)

The distilled ethyl 2-, 3- or 4-pyridyl acetate (**163**, 3.30 g, 20 mmol), sodium hydride (1.84 g, 80 mmol) and **162b** (R = CH_3, 3.4 g, 20 mmol) were heated at reflux in dry THF (100 ml) using the method described under Procedure I. The products were purified by silica gel TLC using chloroform : methanol (7 : 1 v/v) as development solvent. The physical and analytical data for **164d-n** are presented in Table 15, whereas the IR and ^1H NMR spectral data are summarized in Table 16. ^{13}C NMR spectral data for **164g**, **h**, **j**, and **n** are presented in Table 17.

4.4.4.2.1.0. 1-Methyl-4-propionyl-4-(4-pyridyl)piperidine (160c) and 1,3-dimethyl-4-propionyl-(pyridyl)piperidines (160 d, f, and h) General Procedure J

To a solution of **164c** (0.248 g, 1.0 mmol) in dry THF (10 ml) at 0 °C, ethylmagnesium bromide (1.134 g, 1.0 mmol) in ether (3M) was added slowly with stirring under a nitrogen atmosphere. The reaction was allowed to proceed at 0 °C for 8 hr. Saturated ammonium chloride (10 ml) was added with external cooling and stirring was continued for 6 hr. The organic layer was separated and the aqueous layer was basified with 20 % sodium hydroxide prior to extraction with chloroform (3 x 30 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed *in vacuo* at 40 °C. The oil-like residue was purified by silica gel TLC using chloroform : methanol (1:1 v/v) as development solvent. Extraction of the band having Rf 0.35 afforded **160c** as an oil (80 mg, 30%). Compounds **160d, h** were synthesized by reaction of the corresponding ester **164d, k** respectively, with ethylmagnesium bromide according to Procedure J at reflux temperature in dry THF for 24 hr. The products were purified using the procedure described for **160c** (**164d**, Rf 0.6; **164h**, Rf 0.51). The chemical yields of **160d, h** were 65 and 50 % respectively. The physical and spectral data for compounds **160c, d** and **h** are presented in Tables 13 and 14, respectively.

4.4.4.2.2.0. 4-Ethoxycarbonyl-1-methyl-4-(1,2-, 1,4- or 1,6-dihydro-1-methoxycarbonyl-2(4- or 6)-alkyl-3-pyridinyl)piperidines (167a, b, 168a, b and 169a, b)

To a solution of ethyl 1-methyl-4-(3-pyridyl)piperidine-4-carboxylate (**164b**, 0.248 g, 1.0 mmol) in dry THF (20 ml) at -78 °C, methyl chloroformate (0.113 g, 1.2 mmol) was added with stirring under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 1 hr. Methylmagnesium chloride (1.2 mmol) in THF (3 M solution) was added slowly. The reaction was allowed to warm to 0 °C and proceed for 30 minutes at this temperature. Saturated ammonium chloride (10 ml) was added. The organic layer was separated and the aqueous layer was basified with aqueous NaOH (20 % v/v) and extracted with chloroform (2 x 20 ml). The combined organic fractions were dried ($MgS0_4$) and the solvent was removed *in vacuo* at 25 °C. The viscous product (0.177 g, 55 %) was a mixture of 4-ethoxycarbonyl-1-methyl-4-(1,2-dihydro-1-methoxycarbonyl-2-methyl-3-pyridyl)piperidine (**167a**), 4-ethoxycarbonyl-1-methyl-4-(1,4-dihydro-1-methoxycarbonyl-4-methyl-3-pyridyl)piperidine (**168a**) and 4-ethoxycarbonyl-1-methyl-4-(1,6-dihydro-1-methoxycarbonyl-6-methyl-3-pyridyl)piperidine (**169a**), in the ratio 3 : 1 : 7 (calculated from the integrals of dihydropyridine ring proton chemical shifts for the ^1H NMR spectrum of the mixture run in DMSO-d_6, at 75 °C) which could not be separated by TLC (Rf, 0.63, silica gel, $CHCl_3$: MeOH, 1 : 1 v/v). Anal. calcd. for $C_{34}H_{54}N_4O_8Cl_6Pt.H_2O$; C: 38.07; H: 5.26; N: 5.20; Found; C: 38.19; H: 5.13; N: 5.19. The spectral data for compounds **167a**, **168a** and **169a** are summarized in Table 19.

A similar reaction using n-butylmagnesium chloride also afforded an inseparable mixture (Rf, 0.85, silica gel, $CHCl_3$: MeOH, 1 : 1 v/v) of 1,2-, 1,4- and 1,6-dihydropyridine products **167b**, **168b** and **169b** respectively (0.277 g, 76 %) in the ratio 1 : 1.5 : 5 (calculated from the integrals of dihydropyridine ring proton chemical shifts for the ^1H NMR spectrum of the mixture run in DMSO-d_6, at 75 °C). The spectral data for compounds **163b**, **164b** and **165b** are also summarized in Table 18.

4.4.4.2.3.0. 4-Ethoxycarbonyl-1-methyl-4-(1,6-dihydro-1-acyl(acyloxy)-6-phenyl-3-pyridinyl)piperidines (169c-f)

To a solution of ethyl 1-methyl-4-(3-pyridyl)piperidine-4-carboxylate (**164b**, 0.248 g, 1.0 mmol) in dry THF (20 ml) at -78 ^{o}C, methyl chloroformate (0.113 g, 1.2 mmol) or phenyl chloroformate (0.19 g, 1.2 mmol) was added with stirring under a nitrogen atmosphere. The reaction was stirred at -78 ^{o}C for 1 hr. Phenylmagnesium chloride (1.2 mmol) in THF (2 M solution) was added slowly. The reaction was allowed to warm to 0 ^{o}C and proceed for 30 minutes at this temperature. The work-up procedure was the same as described in section **4.4.4.2.2.0.**. The product was purified by silica gel TLC using chloroform : methanol (7 : 1 v/v) as development solvent. The physical and spectral data for **169c-f** are summarized in Tables 19 and 20, respectively.

4.4.4.2.4.0. 4-Ethoxycarbonyl-1-methyl-(1,2-dihydro-1-phenoxycarbonyl-4-pyridinyl)piperidine (171a).

Phenyl chloroformate (0.19 g, 1.2 mmol) was added with stirring to a solution of ethyl 1-methyl-4-(4-pyridyl)piperidine-4-carboxylate (**164c**, 0.248 g, 1.0 mmol) in dry methanol (20 ml) at -78 ^{o}C, under a nitrogen atmosphere. Sodium borohydride (0.38 g, 10 mmol) was added to the resulting white suspension in small aliquots as described in Procedure F. The oil-like product **171a** was purified by silica gel TLC using chloroform : methanol (7 : 1 v/v) as development solvent (Rf = 0.67). The physical and spectral data for **171a** are presented in Tables 19 and 20, respectively.

4.4.4.2.5.0. 4-Ethoxycarbonyl-1-methyl-4-(1,2-dihydro-1-acyl(acyloxy)-2-alkyl(phenyl)-4-pyridinyl)piperidines (171b-m)

A solution of ethyl 1-methyl-4-(4-pyridyl)piperidine-4-carboxylate (**164c**, 0.248 g, 1.0 mmol) in dry THF (20 ml) was allowed to react with 1.2 mmol of a chloroformate (methyl or phenyl chloroformate) or an acid chloride (acetyl or benzoyl chloride) and 1.2

mmol of a Grignard reagent (methyl, *n*-butyl or phenylmagnesium chloride) using the procedure described in Section **4.5.5.1.0.0.**. Purification was carried out as described for compounds **169c-f**. The physical data for compounds **171b-m** are presented in Table 19 and the spectral data are summarized in Table 20.

4.4.5.0.0.0. 8-[2-(Pyridyl)ethyl]-1,4-dioxa-8-azaspiro[4.5]decanes (175 a and c).

To a solution of 1,4-dioxa-8-azaspiro[4.5]decane (**172**, 3.58 g, 25 mmol), 2- or 4-vinylpyridine (2.625 g, 25 mmol) in dry methanol (50 ml), glacial acetic acid (1.5 g, 25 mmol) was added and the mixture was heated at reflux for 10 hr. The solvent was removed *in vacuo* at 40 ^{o}C and the product was recrystallized from ethyl acetate : hexane (4 : 1 v/v). The isolated yields were: **175a**, 5.6 g (90 %); **175c**, 5.77 g (93 %). Physical and spectral data for **175a** and **b** are presented in Tables 22 and 23, respectively.

4.4.5.1.0.0. 2-(3-Pyridyl)ethanol.

Purified paraformaldehyde (4 g) was added with stirring to a solution of 3-picolyl lithium (25 mmol) and hexamethylphosphoric triamide (HMPT, 4.5 g) in dry THF (20 ml) prepared according to the method of Kaiser and Petty[367], at 0 ^{o}C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 25 ^{o}C prior to heating at reflux for 4 hr. The reaction mixture was cooled to 0 ^{o}C and 10 % HCl (50 ml) was added dropwise with stirring. The aqueous layer was separated, basified with aqueous sodium hydroxide (20 % w/v), and extracted with chloroform (4 x 80 ml). The combined chloroform extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* at 40 ^{o}C. The oil-like residue was distilled. The fraction collected at 80-84 ^{o}C (1.8 mm Hg) was purified by silica gel column chromatography using ethyl acetate : methanol (9 : 1 v/v) as eluent to afford 2-(3-pyridyl)ethanol (60 % yield) that also contained HMPT (10 % of the total weight of 2.04 g).The spectral data were as follows: IR (neat): 3303 cm^{-1}(br, OH);

^{1}H NMR ($CDCl_3$), δ: 2.86 (t, J = 6.5Hz, 2H, $CH_2\mathit{CH_2}$ -Pyr), 3.9 (t, J = 6.5Hz, 2H, $CH_2\mathit{CH_2}$ OH), 4.4 (s, 1H, OH, exchanges with D_2O), 7.25 (d, J = 5Hz of d, J = 8.5Hz, pyridine H-5), 7.6 (d, J = 8.5Hz, IH, pyridine H-4), 8.4-8.5 (m, 2H, pyridine H-6, H-2).

4.4.5.1.1.0. 2-(3-Pyridyl)ethyl mesylate

Methanesulfonyl chloride (0.87 g, 7.1 mmol) was added dropwise with stirring to a solution of 2-(3-pyridyl)ethanol (0.81 g, 4.7 mmol) and dry triethylamine (0.72 g, 7.1 mmol) in dichloromethane (50 ml) at 0 °C, under a nitrogen atmosphere. The mixture was allowed to stir for 6 hr at 0 °C prior to filtration. The filtrate was washed with distilled water (2 x 20 ml), dried (Na_2SO_4) and the solvent was removed *in vacuo* at 40 °C to afford the product as a yellow oil (1.38 g, 97 %); ^{1}H NMR ($CDCl_3$), δ: 2.9 (s, 3H, SO_2Me), 3.05 (t, J = 6.5Hz, 2H, $CH_2\mathit{CH_2}$-*Pyr*), 4.45 (t, J = 6.5Hz, 2H, $CH_2\mathit{CH_2}$OH), 7.3 (m, 1H, pyridine H-5), 7.6 (d, J = 8.5Hz, 1H, pyridine H-4), 8.5-8.63 (m, 2H, pyridine H-6, H-2).

4.4.5.2.0.0. 8-[2-(3-Pyridyl)ethyl]-1,4-dioxa-8-azaspiro[4.5]decane (175b)

2-(3-Pyridyl)ethyl mesylate (**174**, 2.01 g, 10 mmol) and 1,4-dioxa-8-azaspiro[4.5]decane (1.43 g, 10 mmol) in dry acetonitrile (100 ml) was heated at reflux in the presence of anhydrous potassium carbonate (2.76 g, 20 mmol) for 10 hr. The solid was filtered off, the solvent removed *in vacuo* at 25 °C, and the product was recrystallized from ethyl acetate : hexane (3 : 1 v/v) to afford **175b** (1.36 g, 55 %). The physical and spectral data for **175b** are presented in Tables 22 and 23, respectively.

4.4.5.3.0.0. 1-[2-(Pyridyl)ethyl]-4-piperidones (176a-c)

The appropriate 8-(2-(pyridyl)ethyl)-1,4-dioxa-8-azaspiro[4.5]decane (**175a-c**, 2.48 g, 10 mmol) was heated at reflux in 10% hydrochloric acid (100 ml) for 12 hr. After cooling, the solution was basified with solid sodium carbonate and extracted with chloroform (3 x 100 ml). Drying the combined chloroform extracts (Na_2SO_4) and removal of the solvent *in vacuo* at 40 ^{o}C afforded the respective products **176a-c** as viscous oils. The isolated yields were: **176a** (1.94 g, 90 %), **176b** (1.73 g, 85%) and **176c** (1.86 g, 91 %). The spectral data for **176a-c** are summarized as follows:

176a: IR (neat): 1716 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$), δ: 2:45 (t, J = 6Hz, 4H, H-3, H-5), 2.86-3.06 (m, 8H, H-2, H-6, CH_2CH_2-Pyr), 7.1-7.3 (m, 2H, pyridine H-3 and H-5), 7.65 (d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.60 (d, J = 5.5Hz, 1H, pyridine H-6).

169b: IR (neat): 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$), δ: 2.46 (t, J = 6Hz, 4H, H-3, H-5), 2.65-2.90 (m, 8H, H-2, H-6, CH_2CH_2-Pyr), 7.2 (d, J = 8Hz of d, J = 5Hz, 1H, pyridine H-5), 7.55 (d, J = 8Hz, 1H, pyridine H-4), 8.5 (m, 2H, pyridine H-2, H-6).

169c: IR (neat): 1712 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$), δ: 2.45 (t, J = 6Hz, 4H, H-3, H-5), 2.7-2.9 (m, 8H, H-2, H-6, CH_2CH_2-Pyr), 7.18 (d, J = 6Hz, 2H, pyridine H-3, H-5), 8.52 (d, J = 6Hz, 2H, pyridine H-2, H-6).

4.4.5.4.0.0. 1-[2-(Pyridyl)ethyl]-4-[(*N*-phenyl)amino]piperidines (178a-c)

A solution of 1-[2-(2-pyridyl)ethyl]-4-piperidone (**176a**, 3.9 g, 19 mmol) and dry aniline (2.8 g, 30 mmol) in dry toluene (70 ml) was heated at reflux for 2.5 hr in the presence of a few crystals of *p*-toluenesulfonic acid (TsOH), with concomitant azeotropic removal of water. The solvent was removed *in vacuo* at 40 ^{o}C and the resulting imine intermediate product **177** was dissolved in dry methanol (50 ml) prior to cooling to 0 ^{o}C.

$NaBH_4$ (2.5 g, 66 mmol) was added slowly in small aliquots with cooling (ice-water bath). The reaction was allowed to proceed at 0 °C for 6 hr, and then poured onto crushed ice (60 g). The resulting mixture was extracted with chloroform (4 x 80 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* at 40 °C. The viscous oil obtained was recrystallized from ethyl acetate : hexane (2 : 1 v/v) to yield **178a** (3.5 g, 65 %). A similar procedure was used to prepare **178b** (64 %) and **171c** (62 %). The physical and spectral data for **178a-c** are summarized in Tables 22 and 23, respectively. The spectral data for the imine intermediates **177a-c** are summarized as follows:

177a, IR (neat): 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$), δ: 2.25-3.1 (m, 12H, H-2, H-6, H-3, H-5, *CH*$_2$*CH*$_2$-Pyr), 6.73 (m, 3H, *o*- and *p*-phenyl hydrogens), 6.97-7.4 (m, 4H, *m*-phenyl hydrogens, pyridine H-3, H-5), 7.6 (d, J = 8Hz of d, J = 8Hz, 1H, pyridine H-4), 8.56 (d, J = 5Hz, 1H, pyridine H-6).

177b, IR (neat): 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$), δ: 2.3-2.9 (m, 12H, H-3, H-5, H-2, H-6, *CH*$_2$*CH*$_2$-Pyr), 6.7 (m, 3H, *o*- and *p*-phenyl hydrogens), 7.2 (m, 3H, *m*-phenyl hydrogens, pyridine H-5), 7.55 (d, J = 8Hz, 1H, pyridine H-4), 8.5 (m, 2H, pyridine H-2, H-6).

177c, IR (neat): 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$), δ: 2.3-2.9 (m, 12H, H-3, H-5, H-2, H-6, *CH*$_2$*CH*$_2$-Pyr), 6.75 (m, 3H, *o*- and *p*-phenyl hydrogens), 7.0-7.4 (4H, *m*-phenyl hydrogens, pyridine H-3, H-5), 8.53 (d, J = 6Hz, 2H, pyridine H-2, H-6).

4.4.5.5.0.0. 1-[2-(Pyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidines (179a-c).

1-[2-(2-Pyridyl)ethyl]-4-(*N*-phenyl)aminopiperidine (**178a**, 0.35 g, 1.25 mmol) was dissolved in freshly distilled propionic anhydride (20 ml) and the solution was stirred at 25 °C for 36 hr. Hexane (20 ml) was added and the mixture was placed in a refrigerator. The product which crystallized was washed with hexane and recrystallized from ethyl acetate : hexane (1 : 2 v/v) to afford **179a** (0.4 g, 95%). A similar procedure was used to prepare **179b** (97%) and **179c** (80%). Physical and spectral data for **179a-c** are presented in Tables 22 and 23, respectively.

4.4.5.5.1.0. 1-[2-(1,6-Dihydro-1-phenoxycarbonyl-6-phenyl-3-pyridinyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidine (180).

Phenyl chloroformate (0.19 g, 1.2 mmol) was added dropwise to a solution of 1-[2-(3-pyridyl)ethyl]-4-(*N*-phenyl-*N*-propionyl)aminopiperidine (**179b**, 0.337 g, 1.0 mmol) in dry THF (20 ml) at -78 °C under a nitrogen atmosphere. The reaction was stirred at -78 °C for 1 hr. . Phenylmagnesium chloride (1.2 mmol) in THF (2 M solution) was added slowly. The reaction was allowed to warm to 0 °C and proceed for 20 min. at this temperature. Saturated NH_4Cl solution (10 ml) was added. The organic layer was separated and the aqueous layer was basified with NaOH (20 % w/v) and extracted with chloroform (2 x 30 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed *in vacuo* at 25 °C. The viscous residue obtained was purified by silica gel TLC using ethyl acetate as development solvent (Rf 0.6). The physical and spectral data for **180** are summarized in Tables 24 and 25, respectively.

4.4.5.5.2.0. 1-[2-(1,2-Dihydro-1-phenoxycarbonyl-4-pyridinyl)ethyl]-4-[(N-phenyl-N-propionyl)amino]piperidine (181a)

Phenyl chloroformate (0.19 g, 1.2 mmol) was added to a solution of 1-[2-(4-pyridyl)ethyl]-4-[(*N*-phenyl-*N*-propionyl)amino]piperidine (**179c**, 0.337 g, 1.0 mmol) in dry methanol (ml) at -78 °C under a nitrogen atmosphere with stirring. Sodium borohydride (0.38 g, 10 mmol) was then added in small aliquots as described in Procedure F. The product **181a**, was purified by silica gel TLC using ethyl acetate as development solvent (Rf 0.56) and recrystallized from ethyl acetate : hexane (1 : 1 v/v). The physical and spectral data are presented in Tables 24 and 25, respectively.

4.4.5.5.3.0. 1-[2-(1,2-Dihydro-1-phenoxycarbonyl-6-alkyl(phenyl)-4-pyridinyl)ethyl]-4-[(N-phenyl-N-propionyl)amino]piperidines (181b-d)

Phenyl chloroformate (0.19 g, 1.2 mmol) was added to a solution of 1-[2-(4-pyridyl)ethyl]-4-(N-phenyl-n-propionyl)aminopiperidine (**179c**, 0.337 g, 1.0 mmol) in dry THF (20 ml) with stirring at -78 ^{o}C under a nitrogen atmosphere. The reaction was stirred at -78 ^{o}C for 1 hr. Phenylmagnesium chloride (1.2 mmol) in THF (2 M solution) was added according to the procedure described in section **4.4.5.5.1.0.**. The viscous oil residues obtained were purified by silica gel TLC using ethyl acetate as development solvent. The Rf values for the products were: **181b**, 0.59; **181c**, 0.68; **181d**, 0.64. The physical and spectral data for compounds **181b-d** are summarized in Tables 24 and 25, respectively.

4.5.0.0.0.0. ANTINOCICEPTIVE ASSAY

Antinociceptive (analgesic) activity was determined using the 4% sodium chloride-induced writhing assay reported by Fukawa *et al.*.[372] Five male Sprague-Dawley rats, five weeks old and weighing between 130-180 g, were used for each test dose. Two hours prior to administration of the test compound, the number of writhing responses induced in each rat in the three minute interval, after injection of a 4% sodium chloride solution at a dose of 1 ml/kg ip, were recorded. The test compound was dissolved or solubilized with 10% v/v Tween 80 in physiological saline solution (0.9 % w/v aqueous NaCl) before administration. After administration of the test dose, each rat was again challenged with a 4% sodium chloride solution (1 ml/kg ip) at intervals of 30 and 60 minutes from the time of test compound administration. The number of writhing responses elicited at each time in the three minute period following each challenge was recorded. The lower of the two response counts at the 30 or 60 minute interval was subtracted from the initial number of control writhing responses at the same time interval for each animal and the percentage inhibition, which is a measure of analgesic activity, was calculated using the formula shown below (Eq.31). The ED_{50} and the 95% confidence intervals for compounds tested at multiple doses was determined using the method of Litchfield and Wilcoxon.[380] Single dose test results are reported as the mean % inhibition ± the standard error of the mean (SEM) for five animals.

$$\% \text{ Inhibition} = \frac{W_1-W_2}{W_1} \qquad \text{Eq. 31}$$

where W_1 is number of initial (control) writhing responses and W_2 is the lower of the numbers of writhing responses at either 30 or 60 minutes.

5.0.0.0.0.0. REFERENCES

1. R. J. Flower, S. Moncada and J. R. Vane, in " The Pharmacological Basis of Therapeutics", 7th Edn., (A. G. Gilman , L. S. Goodman, T. W. Rall and F. Murad, eds.), p. 674, MacMillan , New York, 1985.
2. J. H. Jaffe and W. R. Martin, in " The Pharmacological Basis of Therapeutics", 7th Edn., (A. G. Gilman , L. S. Goodman, T. W. Rall and F. Murad, eds.), p. 491, MacMillan Publishing Company, New York, 1985.
3. D. Lednicer in "Central Analgesics", (D. Lednicer, ed.), p. 137, J. Wiley & Sons, Toronto, 1982.
4. F.W. Serturner, *Tronnsdorf's J. Pharm.*, **14**, 47 (1806).
5. A.F. Casy and R.T. Parfitt, "Opioid Analgesics: Chemistry and Receptors", Plenum Press, New York, 1986.
6. G.R. Lenz, D.E. Walters, S.M. Evans and A.J. Hopfinger, "Opiates ", Academic Press, Orlando, Florida, 1986.
7. J.M. Gullard and R. Robinson, *J. Chem. Soc.*, 980 (1923).
8. M. Gates and G. Tschudi, *J. Am. Chem. Soc..*, **74**, 1109 (1952).
9. M. Gates and G.Tschudi, *J. Am. Chem. Soc..*, **78**, 1380 (1956).
10. M. Gordon, *Ann. Rep. Med. Chem.*, **9**, 38 (1974).
11. G. Ginsburg, "The Opium Alkaloids," Wiley (Interscience), New York, 1962.
12. K. W. Bentley, in "Chemistry of the Alkaloids", (S. W. Pelletier, ed.), p.117, Van Nostrad Reinhold, New York , 1970.
13. C. I. Wright, *J. Pharmacol. Exp. Ther.*, **71**, 164 (1947).
14. E. L. Way, J. W. Kemp, J. M. Young and D. R. Grassetti, *J. Pharmacol. Exp. Ther.*, **129**, 144 (1960).
15. E. L. Way, J. W. Kemp and J. M. Young, *Bull. Narc.*, **17**, 15 (1965).
16. U. Weiss, *J. Am. Chem. Soc.*, **77**, 5891 (1955).
17. J. Knoll, S. Furst and K. Kelemen, *J. Pharm. Pharmacol.*, **25**, 929 (1973).

18. L. Small, H. M. Fitch and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936).

19. L. Small, S. G. Turnbull and H. M. Fitch, *J. Org. Chem.*, **3**, 204 (1939).

20. J. Weijlard and A. E. Erickson, *J. Am. Chem.Soc.*, **69**, 869 (1942).

21. R. L. Clark, A. A. Pessolano, J. Wiejlard and K. P. Pfister, *J. Am. Chem. Soc.*, **75**, 4963 (1953).

22. M. J. Lowenstein, U. K. Patent , 955, 493 (1964); *Chem. Abstr.*, **61**, 4410 (1964).

23. G. F. Blame, A. L. Boura, A. E. Fitzgerald and R. E. Lyster, *Br. J. Pharmacol . Chemother.*, **30**, 11 (1967).

24. K. W. Bentley, A. L. Boura, A. E. Fitzgerald, D. G. Hardy, A. McCoubrey, M. C. Aikman and R. E. Lyster, *Nature* , **206**, 102 (1965).

25. K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **87**, 3267 (1967).

26. J. W. Lewis, K. W. Bentley and A. Cowan, *Ann. Rev. Pharmacol.*, **11**, 249 (1970).

27. J. W. Lewis and M. J. Redhead, *J. Med. Chem.*, **13**, 525 (1970).

28. K. W. Bentley, U. K. Patent, 1,136214 (1968); *Chem. Abstr.*, **70**, 782,185 (1965).

29. J. W. Lewis, K. W. Bentley and A. Cowan, *Ann. Rev. Pharmacol. Toxicol.*, **11**, 241 (1971).

30. J. W. Lewis, M. J. Redhead and A. C. B. Smith, *J. Med. Chem.*, **16**, 9 (1973).

31. J. W. Lewis, *Adv. Biochem. Psychopharmacol.*, **8**, 123 (1974).

32. R. G. Twycross, *Pain*, **3**, 93 (1977).

33. H. Isbell and H. F. Frazer, *J. Pharmacol. Exp. Ther.*, **106**, 397 (1952).

34. D. C. Palmer and M. J. Strauss, *Chem. Rev.*, **77**, 1 (1977).

35. J. Hellerbach, A. Grussner and O. Schnider, *Helv. Chim. Acta* , **39**, 429 (1956).

36. O. Schnider and A. Grussner, *Helv. Chim. Acta* , **34**, 2211 (1951).

37. F. Ionescu, W. Klee and R. Katz, *Life Sci.*, **16**, 1793 (1975).

38. J. Hellerbach, O. Schnider, H. Bensendorf and B. Pellmont, "Synthetic Analgesics, Part II (A)", Pergamon Press, Oxford, 1966.

39. E. Costa and P. Greengard, *Adv. Biochem. Psychopharmacol.*, **8**, 45 (1973).

40. A. Grussner, J. Hellerbach and O. Schnider, *Helv. Chim. Acta* , **40**, 1232 (1957).

41. J. Hellerbach, A. Grussner and O. Schnider, U. K. Patent , 843,752 (1960); *Chem. Abstr.*, **55**, 4544 (1961).

42. A. E. Jacobson, K. C. Rice, J. Reden, L. Lupinacci, A. Brossi, R. A. Streaty and W. A. Klee, *J. Med. Chem.*, **22**, 328 (1979).

43. N. B. Eddy and E. L. May, *Science* , **181**, 407 (1973).

44. E. L. May, *J. Med. Chem.*, **23**, 225 (1980).

45. N. B. Eddy and E. L. May, "Synthetic Analgesics, Part II (B)", Pergamon Press, Oxford, 1966.

46. E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

47. E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

48. E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 295 (1959).

49. M.P. Wenntland, N. F. Albertson and A. K. Pierson, *J. Med. Chem.*, **23**, 71 (1980).

50. N. F. Albertson, *J. Med. Chem.*, **18**, 619 (1975).

51. M. Gordon, J. J. Lafferty, D. H. Tedeshi, B. M. Sutton, N. B. Eddy and E. L. May, *J. Med. Chem.*, **5**, 633 (1962).

52. R. S. Zukin and S. R. Zukin, *Trends in Neurosci.*, **7**, 160 (1984).

53. O. Eisleb and O. Schaumann, *Dtsch. Med. Wochschr.*, **65**, 967 (1939); *Chem. Abstr.*,**33**, 9442 (1939).

54. L. Lasagna and H. K. Beecher, *J. Pharmacol. Exp. Ther.*, **112**, 306 (1954).

55. N. B. Eddy, H Halbach and O. J. Braenden, *Bull. WHO* , **14**, 353 (1954).

56. V. F. Mauro, M. F. Bonfiglio and A. L. Spunt, *Clin. Pharm.*, **5**, 837 (1986).

57. Martindale: "The Extra Pharmacopoeia ", 28 th Edn., p. 1026, The Pharmaceutical Press, London, 1982.

58. N. B. Eddy, H. Halbach and O. J. Braenden, *Bull. WHO* , **17**, 569 (1957).

59. D. J. Edwards, C. K. Svensson, J. P. Visco, and D. Lalka, *Clin. Pharmacokinet.*, **7**, 421 (1982).

60. C. E. Inturrisi and J. G. Umans, *Clin. Anaesthesiol.*, **1**, 123 (1983).

61. D. L. Larson and P.S. Portoghese, *J. Med. Chem.*, **19**, 16 (1976).

62. C. B. Pert and S. H. Snyder, *Mol. Pharmacol.*, **10**, 868 (1974).

63. M. M. Abdel-Momen and P. S. Portoghese, *J. Pharm. Pharmacol.*, **23**, 875 (1971).

64. O. Eisleb, *Chem. Ber.*, **74**, 1433 (1941).

65. F. Bergel and A. L. Morrison, *Quart. Rev. (London)* , **2**, 345 (1948).

66. R. H. Thorp and E. Walton, *J. Chem. Soc.*, 559, (1948).

67. A. W. D. Avison and A. L. Morrison, *J. Chem. Soc.*, 1471 (1950).

68. A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

69. P. A. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960).

70. P. A. Janssen, *Br. J. Anaesthesiol.*, **34**, 260 (1962).

71. A. F. Casy, M. M. A. Hassan, A. B. Simmonds and D.Staniforth, *J. Pharm. Pharmacol.*, **21**, 434 (1969).

72. W. F. M. Van Bever, C. J. E. Niemegeers and P. A. J. Janssen, *J. Med. Chem.*, **17**, 1047 (1974).

73. E. Nilsson and P. A. J. Janssen, *Acta. Anaesth. Scand.*, **5**, 73 (1961).

74. C. W. Gorodetzky and W. R. Martin, *Clin. Pharmacol. Ther.*, **6**, 731 (1965).

75. J. P. Tollenaere, H. Moereels and M. Van Loon, *Prog. Drug Res.*, **30**, 91 (1986).

76. W. F. M. Van Bever, K. H. L. Schellekens, C. J. E. Niemegeers and P. A. J. Janssen, *Arzneim-Forsch. (Drug Res.)* , **26**, 1551 (1976).

77. C. J. E. Niemegeers and P. A. J. Janssen, *Drug Dev. Res.*, **1**, 83 (1981).

78. J. D. Borel, *Contemp. Anaesth. Pract.*, **7**, 1 (1983).

79. P. G. Van Daele, M. F. L. De Bruyn, J. M. Boey, S. Sanszuk, J. T. M. Agten and P. A. J. Janssen, *Arzneim. Forsch.*, **26**, 1521 (1976).

80. J. R. Bagley, R. L. Wynn, F. G. Rudo, B. M. Doorley, H. K. Spencer and T. Spaulding, *J. Med. Chem.*, **32**, 663 (1989).

81. P. A. J. Janssen," Synthetic Analgesics, Part 1, Diphenylpropylamines", Pergamon Press, New York, 1984.

82. K. Blum, " Handbook of Abusable Drugs", Gardner Press, New York, 1984.

83. A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **75**, 4458 (1953).

84. W. B. Wright, Jr. and R. A . Hardy, Jr., *J. Med. Chem.*, **6**, 128 (1953).

85. R. Hiltman, F. Hoffmeister, E. Niemers, U. S. Schlichting and H. Wollweber, *Arzneim. Forsch.*, **24**, 584 (1974).

86. H. Wollweber, *Eur. J. Med. Chem.*, **17**, 125 (1982).

87. J. Hughes, T. W. Smith, B. Morgan and L. Fothergill, *Life Sci.*, **16**, 1753 (1975).

88. J. Hughes, T. W. Smith, H. W. Kosterlitz, L. A. Fothergill, B. A. Morgan and H. R. Morris, *Nature* , **258**, 577 (1975).

89. J. D. Belluzi, N. Grant, V. Garsky, D. Sarantakis, C.D.Wise and L. Stein, *Nature* , **260**, 625 (1976).

90. Y. Audigier, B. Malfroy and J. C. Schwartz, *Eur. J. Pharmacol.*, **41**, 247 (1977).

91. B. P. Rogues, M. C. Fournier-Zaluski, E. Soroca, J. M. Leconte, B. Malfroy, C. Llorens and J. C. Schwartz, *Nature* , **288**, 286 (1980).

92. C. H. Li and D. Chung, *Proc. Natl. Acad. Sci. U. S. A.*, **73**, 1145 (1976).

93. A. Goldskin, W. Fischil, L. I. Lowney, M. Hunkapiller and L. Hood, *Proc. Natl. Acad. Sci. U. S. A.*, **78**, 7291 (1981).

94. I. Kitchen, *Gen. Pharmacol.*, **16**, 79 (1985).

95. P. W. Schiller, in "Peptides: Analysis, Synthesis, Biology", (S. Udenfriend and J. Meinhofer, Eds.), p. 220, Academic Press, New York, 1984.

96. J. Posner, K. Dean, S. Jeal, G. Moody, A. W. Peck, G. Rutter and A. Talekas, *Br. J. Clin. Pharmacol.*, **24**, 266P (1987).

97. N. B. Eddy, *Chem . Ind. (London)*, 1462 (1959).

98. A. Brossi, H. Besendorf, L. A. Pirk and A. Rheinier, Jr., in "Analgetics", (G.DeStevens, ed.) p. 281, Academic Press, New York, 1965.

99. D. Lednicer and P.F. Von Voigtlander, *J. Med. Chem.*, **22**, 1157 (1979).

100. W. Von Lintz, S. Erlacin, E. Frankus and H. Uragg, *Arzneim. Forsch.*, **31**, 1932 (1981).

101. J. P. Yardley, H. Fletcher and P. B. Russell, *Experientia* , **34**, 1124 (1978).

102. C. R. Clark, P. R. Halfpenny, R. G. Hill, D. C. Horwell, J. Hughes, T. C. Javis, D. C. Rees and S. Schofield, *J. Med. Chem.*, **31**, 521 (1988).

103. H. Nakamura, K. Ishi, Y. Kokoyama, S. Notoyoshi, K. Natsuka and M. Shimizu, *J. Pharm. Pharmacol.*, **32**, 635 (1980).

104. K. Natsuka, H. Nakamura, Y. Nishikawa, T. Negoro, H. Uno and H. Nishimura, *J. Med. Chem.*, **30**, 1779 (1987).

105. B. T. Finncane, J. B. Floyd, D. J. Petro and R. Braswell, *Can. Anaesth. Soc. J.*, **29**, 500 (1982), and refs. cited therein.

106. D. M. Zimmermann, B. E. Cantrell, J.K. Swartzendruber, N. D. Jones, L. G. Mendelsohn, J. D. Leander and R. C. Nickander, *J. Med. Chem.*, **31**, 555 (1988).

107. E. L. May, *Pharmacol. Res. Commun.*, **9**, 197 (1977).

108. E. Rekka and P. Kourounakis, *Eur. J. Med. Chem.*, **24**, 179 (1989).

109. R. N. Booker, S. E. Smits, W. W. Turner, Jr. and A. Pohland, *J. Med. Chem.*, **20**, 885 (1977).

110. A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986, (1954).

111. P. R. Andrews and E. J. Lloyd, *Med. Res. Rev.*, **2**, 355 (1982).

112. N. L. Allinger and Y. H. Yuh, *Quantum Chem. Progr. Exch.*, **13**, 395 (1980).

113. M. Froimwitz, *J. Med. Chem.*, **25**, 1127 (1982).

114. R. Franke, in "Theoretical Drug Design Methods", (R. Franke, ed.), p. 315, Elsevier, New York, 1984.

115. A. S. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, **29**, 257 (1977).

116. J. J. Kauffman, in "Advances in Endogenous and Exogenous Opioids: Proceedings of the 12th International Narcotics Research Conference", (T. Hiroshi and E. J. Simond, Eds.), p. 147, Kodausha, Tokyo, 1981.

117. E. J. Lien, G. L. Tong, D. B. Srulevitch and C. Dias, *NIDA Res. Mon.*, No. 22, p. 186 (1978).

118. C. - Y. Cheng, E. Brochmann - Hanssen and J. A. Waters, *J. Med. Chem.*, **25**, 145 (1982).

119. E. J. Simon, J. M. Miller and I. Edelman, *Proc. Natl. Acad. Sci. U. S. A.*, **70**, 1947 (1973).

120. L. Terenius, *Acta Pharmacol. Toxicol.*, **32**, 317 (1973).

121. C. B. Pert and S. H. Snyder, *Science* , **179**, 1011 (1973).

122. "The Opiate Receptors", (G. W. Pasternak, ed.), Humana Press, Clifton, New Jersey, 1988.

123. H. H. Loh, P. Y. Law, T. Ostwald, T. M. Cho and E. L. May, *Fed. Proc.*, **87**, 147 (1978).

124. W. R. Martin, C. G. Eades, J. A. Thompson, R.E. Huppler and P. E. Gilbert, *J. Pharmacol. Exp. Ther.*, **197**, 517 (1976).

125. M. Wuster, R. Schulz and A. Herz, *Neurosci. Lett.*, **15**, 193 (1979).

126. T. Oka, K. Negishi and M. Suda, in "Advances in Endogenous and Exogenous Opioids: Proceedings of the 12th International Narcotics Research Conference", (T. Hiroshi and E. J. Simond, Eds.), p. 21, Kodausha, Tokyo, 1981.

127. J. Grevel and W. Sadee, *Science* , **221**, 1198 (1983).

128. B. L. Wolozin and G. W. Pasternak, *Proc. Natl. Acad. Sci. U. S. A.*, **78**, 6181 (1981).

129. R. A. Lutz, R. A. Cruciani, T. Costa, P. J. Munson and D. Robard, *Biochem. Biophys. Res.Commun.*, **122**, 265 (1984).

130. Y. Audigier, B. Attali, H. Mazurgil and J. Cros, *Life Sci.*, **31**, 1287 (1982).

131. E. J. Simpson, in "Receptor Binding in Drug Research ", (R. A. O'Brien, ed.), p.183, Marcel Dekker, New York, 1986.

132. P. L. Wood and S. Iyengar in "The Opiate Receptors", (G. W. Pasternak, ed.), p. 307, Humana Press, Clifton, New Jersey, 1988.

133. R. J. Knapp, F. Porreca, T. F. Burks and H. I. Yamamura, *Adv. Pain Res.*, **11**, 247 (1989).

134. S. R. Childers and S. H. Snyder, *Life Sci.*, **23**, 759 (1980).

135. G. S. F. Ling, R. Simantov and G. W. Pasternak, *Soc. Neurosci. Abstr.*, **13**, 209, 1987.

136. G. W. Pasternak and E. F. Hahn, *J. Med. Chem.*, **23**, 674 (1980).

137. A. Herz, in "Trends in Medicinal Chemistry: Proceedings of the 9th International Symposium on Medicinal Chemistry, Berlin, 1986", (E. Mutschler and E. Winterfeldt, eds.), p. 337, Weinheim, New York, 1987.

138. J. R. Mathiasen and J. L. Vaught, *Eur. J. Pharmacol.*, **136**, 405 (1987).

139. J. S. Heyman, J. L. Vaught, R. B. Raffa and F. Porreca, *Trends Pharmacol.Sci.*, **9**, 134 (1988).

140. P. S. Portoghese, A. W. Lipkowski and A. E. Takemori, *J. Med. Chem.*, **30**, 238 (1987).

141. G. R. Peters, N. J. Ward, E. G. Antal, P. Y. Lai and E. W. De Maar, *J. Pharmacol. Exp. Ther.*, **240**, 128 (1987).

142. Z. H. Galina and A. J. Kastin, *Life Sci.*, **39**,2153 (1986).

143. M. C. Fournier-Zaluski, G. Gacel, B. Maigret, S. Premilat and B. P. Roques, *Mol. Pharmacol.*, **20**, 484 (1989).

144. P. S. Portoghese, *Trends Pharmacol. Sci.*, **10**, 230 (1989).

145. D. Roner, H. H. Buscher, R. C. Hill, R. Maurer, T. J. Petcher, H. Zenger, W. Benson, E. Finner, W. Milkowski and P. W. Thies, *Nature*, **298**, 759 (1982).

146. M. Yeadom and I. Kitchen, *Neuropharmacol.*, **27**, 345 (1988).

147. V. M. Kolb, *Recent Adv. Drug Res.*, **16**, 281 (1987).

148. A. F. Feinberg, I. Creese and S. H. Snyder, *Proc. Natl. Acad. Sci. U. S. A.*, **73**, 4215 (1976).

149. W. F. Michne, R. L. Salsbury and S. J. Michalee, *J. Med. Chem.*, **20**, 682 (1977).

150. B. V. Cheney, *J. Med. Chem.*, **31**, 521 (1988).

151. V. M. Kolb, *Pharm. Res.*, **4**, 450 (1987).

152. E. F. Hahn, *Med. Res. Rev.*,**5**, 255 (1985).

153. M. R. Johnson and G. M. Milne, *Ann. Rep. Med. Chem.*, **10**, 12 (1975).

154. D. Hammond in "Opiates ",(G.R. Lenz, D.E. Walters, S.M. Evans and A.J. Hopfinger eds.) p. 29, Academic Press, Orlando, Florida, 1986.

155. W. R. Martin, *Pharmacol. Rev.*, **35**, 283 (1984).

156. G. A. Olson, R. D. Olson and A. J. Kastin, *Peptides*, **8**, 1135 (1987).

157. G. A. Olson, R. D. Olson and A. J. Kastin, *Peptides*, **10**, 205 (1989).

158. D. Miller, in "Burger's Medicinal Chemistry ", 4th Edn., (M. E. Wolff, ed.), Part III, p.759, John Wiley and Sons, New York, 1981.

159. I. M. Coupar, *Life Sci.*, **41**, 917 (1987).

160. N. Dafny and N. R. Pellis, *Neuropharmacol.*, **27**, 345 (1988).

161. J. M. Pearl, P. M. Dougherty, K. J. Krajewski and N. Dafny, *Soc. Neurosci. Abstr.*, **12**, 1381 (1986).

162. K. Rambadran and M. Bansinat, *Pharm. Res.*, **3**, 263 (1987).

163. P. L. Wood in " Analgesics: Neurochemical, Behavioral and Clinical Perspectives", (M. Kuhar and G. W. Pasternak, Eds.), p. 175, Raven Press, New York, 1984.

164. H. Blumberg, P. S. Wolf and H. B. Dayton, *Proc. Soc. Exp. Biol. Med.*, **118**, 736 (1965).

165. G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exp. Ther.*, **80**, 300 (1944).

166. F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).

167. T. L. Yaksh, J. C. Yeung and T. A. Rudy, *Brain Res.*, **114**, 83 (1976).

168. H. Tagaki, T. Inukai and M. Nakama, *Jap. J. Pharmacol.*, **16**, 287 (1966).

169. S. L. Wallenstein, in " Analgesics: Neurochemical, Behavioral and Clinical Perspectives", (M. Kuhar and G. W. Pasternak, eds.), p. 235, Raven Press, New York, 1984.

170. R. T. Coutts and A. F. Casy, in " Heterocyclic Compounds: Pyridine and Its Derivatives", (R. A. Abramovitch, ed.), Vol. 14, Suppl. Pt. 4, p. 445, John Wiley and Sons, New York, 1975.

171. H. J. Roth, A. Kleeman and T. Beisswenger, " Pharmaceutical Chemistry, Vol. 1: Drug Synthesis", p. 249, Ellis Horwood, Chichester, England, 1988.

172. A. M. Kofman, V. E. Golender, L. Y. Leitis, K. I. Rubina, M. V. Simanskaya and B. Rosenblit, *Chem. Heterocycl. Comp* ., **21**, 89 (1985).

173. G. Pastelia, R. Mendez, E. Kabela and A. Farah, *Life Sci.*, **33**, 1787 (983).

174. M. R. Pavia, C. P. Taylor, F. M. Hershersoa, S. J. Lobbestael and D. E. Butler, *J. Med. Chem.*, **31**, 841 (1988).

175. M. R. Pavia, C. P. Taylor, and S. J. Lobbestael , *J. Med. Chem.*, **32**, 1237 (1989).

176. R. McCaque, M. Jarman,M. G. Rowlands, J. Mann, C. P. Thickitt, D. W. Clissold, S.Neidle and G. Webster, *J. Chem. Soc. Perkin Trans. I*, 196 (1989).

177. Y. Nishiokawa, T. Shindo, K. Ishii, H. Nakamura, T. Kon and H. Uno, *J. Med. Chem.*, **32**, 583 (1989).

178. W. T. Comer, W. L. Matier and M. S. Amer, in "Burger's Medicinal Chemistry", 4th Edn., (M. E. Wolff, ed.), Part III, p.285, John Wiley and Sons, New York, 1981.

179. J. Kuthan and A. Kurfurst, *Ind. Chem. Eng. Prod. Res. Dev.*, **21**, 191 (1982).

180. E. Shek, T. Higuchi and N. Bodor, *J. Med. Chem.*, **19**, 113 (1976).

181. J. W. Simpkins, J. McCornack, K. S. Estes, M. E. Brewster, E. Shek and N. Bodor, *J. Med. Chem.*, **29**, 1809 (1986).

182. E. Palomino, D. Kesssel and J. P. Horowitz, *J. Med. Chem.*, **32**, 622 (1989).

183. M. J. Phelan, *Diss. Abstr. Int.*, **48**, 2331 (1988).

184. R. T. Coutts and J. R. Scott, *Can. J. Pharm., Sci.*, **6**, 78 (1971).

185. J. K. Landquist, in " Comprehensive Heterocyclic Chemistry", (O. Meth-Cohn, ed.), Vol.1, p. 143, Pergamon Press, Oxford, England, 1984.

186. J. S. Yadav, W. -C. Shang, M. Hermsmeier and T. M. Gund, *J. Med. Chem.*, **32**, 622 (1989).

187. N. Yokoyama, P. I. Almuala, F. B. Block, F. R. Granat, N. Gotfried, R. T. Hill, E.H. McMahon, W. F. Munch, H. Rachlin, J. K. Saeiene, M. G. Siegel, H. C. Tomaselli and F. H. Clarke, *J. Med. Chem.*, **22**, 537 (1979).

188. K. Redda, L. A. Corleto and E. E. Knaus, *Can. J. Chem.*, **57**, 298 (1979).

189. L. A. Cates, V. -S. Li and S. S. Hedge, *Pharm. Res.*, **5**, Suppl., 60 (1988).

190. D. Nisato, M. Frigerio and G. F. Mirando, *Chem. Abstr.*, **101**, 7038 (1984).

191. S. P. Markey and N. R. Schmuff, *Med. Res. Rev.*, 6, 389 (1986).

192. R. E. Heikkila, and P. K. Sonsalla,*Can J. Neuro. Sci.*, **14**, 436 (1987).

193. U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

194. D. M. Stout and A. I. Meyers, *Chem. Rev.*, **82**, 223 (1982).

195. N. C. Cook and J. E. Lyons, *J. Am. Chem. Soc.*, **87**, 223 (1982).

196. R. E. Lyle and G. J. Guathier, *Tetrahedron Lett.*, 4615 (1965).

197. P. S. Anderson and R. E. Lyle, *Adv. Heterocycl. Chem.*, **6**, 45 (1966).

198. J. G. Keay, *Adv. Heterocycl. Chem.*, **39**, 1 (1986).

199. E. Booker and U. Eisner, *J. Chem. Soc. Perkin Trans.* I, 929 (1975).

200. S. -I. Yamada, M. Kuramoto and Y. Kugawa, *Tetrahedron Lett.*, 3101 (1969).

201. J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Commun.*, **29**, 1654 (1964).

202. R. F. Francis, C. D. Crews and B. S. Scott, *J. Org. Chem.*, **43**, 3227 (1978).

203. R. E. Lyle and C. B. Boyce, *J. Org. Chem.*, **39**, 3708 (1974).

204. F. W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).

205. E. Knaus and K. Redda, *Can. J. Chem.*, **55**, 1788 (1977).

206. R. F. Houton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958).

207. D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, **49**, 3392 (1984).

208. A. Caisini, B. DiRienzo, F. M. Moracci, S. Tortorello, F. Liberatore and A. Arnone, *Tetrahedron Lett.*, 2139 (1978).

209. C. S. Giam and E. E. Knaus, *Tetrahedron Lett.*, 4961 (1971).

210. E. Piers and M. Soucy, *Can. J. Chem.*, **52**, 3563 (1974).

211. J. Kuthan, E. Janeckova and M. Havel, *Collect. Czech. Chem. Commun.*, **29**, 143 (1964).

212. D. L. Comins, A. H. Abdullah and N. B. Mantlo, *Tetrahedron Lett.*, **25**, 4867 (1984).

213. H. Bieraugel, K. M. J. Brands and U. K. Pandit, *Heterocycl.*, **27**, 1589 (1988).

214. R. Yamaguchi, Y. Nakazono and T. Matsuki, *Bull. Chem. Soc. Jpn.*, **60**, 215 (1987).

215. M. Masataka, M. Yoshioka and M. Kawanisi, *J. Org. Chem.*, **53**, 3507 (1988).

216. R. Yamaguchi, E. Hata and K. Utimoto, *Tetrahedron Lett.*, **29**, 1785 (1988).

217. D. L. Comins, R. K. Smith and E. D. Stroud, *Heterocycl.*, **22**, 339 (1984).

218. R. A. Abramovitch and E. M. Smith, in " Heterocyclic Compounds: Pyridine and Its Derivatives Part 2", (R. A. Abramovitch, ed.), p. 1, John Wiley and Sons, New York, 1974.

219. E. F. V. Scriven, in " Comprehensive Heterocyclic Chemistry", (A. J. Boulton and A. McKillop, eds.), Vol. 2, Chapter 5, Pergamon Press, Oxford, England, 1984.

220. M. -L. Bennasar, R. Lavilla and J. Bosch, *Heterocycl.*, **27**, 789 (1987).

221. A. Hantzsch, *Justus Liebigs Ann. Chem.*, **215**, 1 (1882).

222. F. Bossert, H. Meyer and E. Wehinger, *Angew. Chem. Int. Ed. Engl.*, **20**, 762 (1981).

223. A. Sausins and G. Duburs, *Heterocycl.*, **27**, 269 (1988).

224. V. Nair, R. J. Offonman, G. A. Turner, A. N. Pryor and N. C. Baenzige, *Tetrahedron*, **44**, 2793 (1988).

225. S. Tanny, J. Grossman and F. W. Fowler, *J. Am. Chem. Soc.*, **94**, 6495 (1972).

226. L. F. Tietze, A. Bergman and K. Bruggeman, *Tetrahedron Lett.*, **24**, 3579 (1983).

227. D. M. Stout, T. Takaya and A. I. Meyers, *J. Org. Chem.*, **40**, 563 (1975).

228. A. Demouldin, H. Gorissen, A. Hesbain-Frisque and L. Ghosez, *J. Am. Chem. Soc.*, **97**, 4409 (1975).

229. Z. Yoshida, H. Hira, S. Miki and S. Yoneda, *Tetrahedron*, **45**, 3217 (1989).

230. T. Shono, Y. Matsumura, O. Onomura and Y. Yamada, *Tetrahedron Lett.*, **28**, 4073 (1987).

231. A. Sausins and G. Duburs, *Heterocycl.*, **27**, 291 (1988).

232. R. M. Kellog, *Angew. Chem. Int. Ed. Eng.*, **23**, 782 (1984).

233. S. Yasui and A. Ohno, *Bioorg. Chem.*, **41**, 70 (1986).

234. W. Traber and R. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958).

235. W. Sliwa, *Heterocycl.*, **14**, 181 (1980).

236. R. E. Lyle, in "Heterocyclic Compounds: Pyridine and its Derivatives", (R. A. Abramovitch, ed.), Vol. 14, Part 1, p. 134, Wiley, New York, 1974.

237. D. L. Comins, A. H. Abdullah and R. K. Smith, *Tetrahedron Lett.*, **24**, 2711 (1983).

238. H. Greuter and H. Schmid, *Helv. Chim. Acta*, **57**, 1204 (1974).

239. R. G. Carlson, *Ann. Rep. Med. Chem.*, **9**, 270 (1974).

240. E. E. Knaus, F. M. Pasutto and C. S. Giam, *J. Heterocycl. Chem.*, **11**, 843 (1974).

241. E. E. Knaus, F. M. Pasutto, C. S. Giam, and E. A. Swinyeard,*J. Heterocycl. Chem.*, **13**, 481 (1976).

242. E. E. Knaus, K. Avasthi and C. S. Giam, *Can. J. Chem.*, **58**, 2447 (1980).

243. G. R. Krow, J. T. Carey, K. C. Cannon and K. J. Henz, *Tetrahedron Lett.*, **23**, 2527 (1982).

244. G. R. Krow, J. T. Carey, D. E. Zacharias and E. E. Knaus, *J. Org. Chem.*, **47**, 1989 (1982).

245. G. R. Krow, R. Raghavachari and R. Siatkowski, *J. Org. Chem.*, **51**, 1916 (1986).

246. S. W. Szcsepansky, Ph. D. Thesis, Temple University, 1985.

247. F. W. Fowler, in "Comprehensive Heterocyclic Chemistry", (A. J. Boulton and A. McKillop, eds.), Vol. 2, p. 365, Pergamon Press, Oxford, 1984.

248. R. Acheson, G. Paglietti and P. Tasker, *J. Chem. Soc. Perkin Trans. I*, 2496 (1974).

249. R. Acheson, and N. Wright, *J. Chem. Soc. Chem. Commun.*, 1421 (1971).

250. G. Adembri, D. Donati, S. Fusi and F. Ponticelli, *Heterocycl.*, **26**, 322 (1987).

251. T. A. Ondrus, E. E. Knaus and C. S. Giam, *Can. J. Chem.*, **57**, 2342 (1979).

252. B. K. Warren and E. E. Knaus, *J. Med. Chem.*, **24**, 462 (1981).

253. T. A. Ondrus, P. R. Pednekar and E. E. Knaus, *Can. J. Chem.*, **63**, 2342 (1985).

254. D. L. Comins and A. H. Abdullah, *Tetrahedron Lett.*, **26**, 43 (1985).

255. D. L. Comins, M. A. Weglarz and S. O'Connor, *Tetrahedron Lett.*, **29**, 43 (1988).

256. D. L. Comins, and M. A. Weglarz, *J. Org. Chem.*, **53**, 4437 (1988).

257. R. A. Abramovitch, A. C. Siani, G. Huttner, L. Zsolnai and J. Miller, *J. Org. Chem.*, **51**, 4739 (1986).

258. F. Liberatore, A. Casini, V. Carelli and R. Mondelli, *J. Org. Chem.*, **40**, 559 (1975).

259. H. C. Van der Plas, "Ring Transformations of Heterocycles",Vol. 2, p. 65, Academic Press, New York, 1973.

260. O. Piepers and R. M. Kellog, *J. Chem. Soc. Chem. Commun.*, 1147 (1980).

261. M. Natsume and M. Ogawa, *Heterocycl.*, **20**, 601 (1983).

262. M. Ferles and J. Pliml, *Adv. Heterocycl. Chem.*, **12**, 43 (1970).

263. A. Silhankova, M. Holik and M. Ferles, *Collect. Czech. Chem. Commun.*, **33**, 2494 (1968).

264. R. Lukes and M. Ferles, *Collect. Czech. Chem. Commun.*, **22**, 121 (1957).

265. A. N. Kost, L. G. Yudin and A. E. Shipov, *Chem. Abstr.*, **52**, 9114 (1958).

266. E. E. Knaus and K. Redda, *J. Heterocycl. Chem.*, **13**, 1237 (1976).

267. M. Holik and M. Ferles, *Collect. Czech. Chem. Commun.*, **32**, 3067 (1967).

268. M. Ferles and M. Holik, *Collect. Czech. Chem. Commun.*, **31**, 2416 (1966).

269. R. E. Lyle and S. E. Mallet, *Ann. N. Y. Acad. Sci.*, **145**, 83 (1967).

270. E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. Stevens and M. Tershima, *J. Org. Chem.*, **33**, 747 (1968).

271. P. M. Quan and L. D. Quin, *J. Org. Chem.*,.**31**, 2487 (1966).

272. S. Oshiro, *J. Pharm. Soc. Jpn.*, **75**, 658 (1955).

273. A. F. Casy, A. H. Beckett, M. A. Iorio and Z. Youssef, *Tetrahedron*, **21**, 3387 (1965).

274. A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, **23**, 1405 (1967).

275. H. Bohme, K. Hartke and A. Muller, *Chem. Ber.*, **96**, 607 (1963).

276. W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **33**, 3622 (1968).

277. S. M. Weinreb and R. R. Staib, *Tetrahedron*, **38**, 3087 (1967).

278. S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, **107**, 1768 (1985).

279. C. J. Schmidle and R. C. Mansfield, *J. Org. Chem.*, **21**, 425 (1956).

280. S. R. Angle and D. O. Arnaiz, *Tetrahedron Lett.*, **30**, 515 (1989).

281. C. Flann, T. C. Malone and L. E. Overman, *J. Am. Chem. Soc.*, **109**, 6097 (1987).

282 K. Clinch, C. J. Marquez, M. J. Parrot and R. Ramage, *Tetrahedron*, **45**, 239 (1989).

283. G. F. Alberici, J. Andrieux, G. Adam and M. M. Plat, *Tetrahedron Lett.*, **24**, 1937 (1983).

284. R. Lukes and J. Jizba, *Collect. Czech. Chem. Commun.*, **19**, 930 (1954).

285. S. Dubey and E. E. Knaus, *Can. J. Chem.*, **61**, 565 (1983).

286. P. Beeken and F. W. Fowler, *J. Org. Chem.*, **45**, 1336 (1980).

287. J. K. Stille and Y. Becker, *J. Org. Chem.*, **45**, 2139 (1980).

288. K. T. Wanner and A. Katner, *Heterocycl.*, **26**, 917 (1987).

289. B. K. Warren and E. E. Knaus, *J. Heterocycl. Chem.*, **25**, 1237 (1988).

290. A. Silkanova, D. Davidova, M. Sputova, P. Trska, D. Vaculikova, D. Vlkova and M.Ferles, *Collect. Czech. Chem. Commun.*, **52**, 1297 (1987).

291. B. K. Warren, Ph. D. Thesis, University of Alberta, Edmonton, 1983.

292. C. -S. Leung, M. G. Rowlands, M. Jarman, A. B. Foster, L. J. Griggs and D. E. V. Wilman, *J. Med. Chem.* , **30**, 1550 (1987).

293. G. W. Pasternak and P. J. Wood, *Life Sci.*, **38**, 1889 (1986).

294. R. B. Rothman. V. Bykov, J. B. Long, L. S. B. E. Jacob, K. C. Rice and J. W. Holaday, *Eur. J. Pharmacol.*, **160**, 73 (1989).

295. G. S. F. Ling, J. M. Macleod, S. Lee, S. H. Lockhart and G. W. Pasternak, *Science*, **226**, 462 (1984).

296. J. G. Topliss, *J. Med. Chem.* , **17**, 799 (1977).

297. C. W. Thornber, *Chem. Soc. Rev.*, **8**, 563 (1979).

298. C. A. Lipinski, *Ann. Rep. Med. Chem.*, **21**, 283 (1986).

299. A. Burger, in, " Medicinal Chemistry" 3rd Edn., (A. Burger, ed.), p. 74, Wiley-Interscience, New York, 1970.

300. A. Korolkovas, "Essentials of Molecular Pharmacology: Background for Drug Design", p. 57, Wiley, New York, 1970.

301. G. W. Hardy, L. A. Lowe, G. Mills, P. Y. Sang, D. S. A. Simpkin, R. L. Follenfant, C. Shankley and T. W. Smith, *J. Med. Chem.* , **32**, 1108 (1989).

302. L. Fieser and M. Fieser, in, "Advanced Organic Chemistry", p. 629, Reinhold Publishing Corporation, New York, 1963.

303. C. Y. Fiakpui and E. E. Knaus, unpublished results.

304. L. Dagnino, M. C. Li-Kwong-Ken, M. W. Wolowyk, H. Wynn, C. R. Triggle and E. E.Knaus, *J. Med. Chem.* , **29**, 2524 (1986).

305. O. M. El-Badry, Ph. D. Thesis, University of Alberta, Edmonton, 1985.

306. E. S. Lazer, H. -C. Wong, G. J. Possanza, A. G. Graham and P. R. Farina, *J. Med. Chem.* , **32**, 100 (1989).

307. T. Kaiho, K. San-nhe, S. Kajiya, T. Suzuki, K. Otsuka, T. Ito, J. Kamiya and M. Maruyama, *J. Med. Chem.* , **32**, 351 (1989).

308 B.Elpern, L. N. Gardner and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

309. A. H. Beckett, A. F. Casy and P. M. Phillips, *J. Med. Pharm. Chem.* , **2**, 351 (1960).

310. L. Berger, A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 904 (1947).

311. H. S. Mosher and J. E. Tessieri, *J. Am. Chem. Soc.*, **73**, 4925 (1951).

312 S. Grossman, U. Moser and E. Mutschler, *Arch. Pharm.*, **311**, 1010 (1978).

313. Y-. Q. Zhu, B. Ge, S. Fang, Y. Zhu, Q. Dai, Z. Tan, Z. Huang and X. Ghen, *Acta Pharm. Sin. (Shanghai)*, **16**, 199 (1981); *Chem. Abstr.*, **95**, 150,311 (1981).

314. C. Chagngying and L. Lemin, *Int. J. Quantum Chem.*, **23**, 1597 (1983).

315. E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, **88**, 297 (1988).

316. "1,3-Dipolar Cycloaddition Chemistry ", (A. Padwa, ed.), Vols. 1 and 2, John Wiley and Sons, New York, 1984.

317. R. Huisgen, R. Grashey and J. Sauer, in "The Chemistry of Alkenes", (S. Patai, ed.), p.79, Wiley-Interscience, London, England, 1964.

318. R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

319. M. K. Meilahn, B. Cox and M. E. Munk, *J. Org. Chem.*, **40**, 819 (1975).

320. K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).

321. K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, **94**, 8953 (1972).

322. A. G. Cook, in, "Enamines: Synthesis, Structure and Reactions", 2nd Edn., (A. G. Cook, ed.), p. 347, Marcel Dekker, New York, 1988.

323. L. M. Thiessen, J. A. Lepoivre and F. C. Alderweireldt, *Tetrahedron Lett.*, 59 (1974).

324. C. S. Giam, E. E. Knaus and F. M. Pasutto, *J. Org. Chem.*, **39**, 3565 (1974).

325. W. O. Moss, R. H. Bradbury, N. J. Hales and T. Gallagher, *Tetrahedron Lett.*, **29**, 6475 (1988).

326. K. R. Henery-Logan and R. A. Clark, *Tetrahedron Lett.*, 801 (1968).

327. S. P. McManus, M. Ortiz and R. A. Abramovitch, *J. Org. Chem.*, **46**, 336 (1981).

328. B. K. Warren and E. E. Knaus, *J. Heterocycl. Chem.*, **24**, 1413 (1987).

329. T. A. Ondrus, M. Sc. Thesis, University of Alberta, Edmonton, 1977.

330. T. J. Maricich, C. N. Angeletakis and R. Mjanger, *J. Org. Chem.*, **49**, 1928 (1984).

331. E. Vilsmaier, R. Adam, P. Altmeier and R. Cronauer, *Tetrahedron*, **45**, 131 (1989).

332. T. Iwakawa, H. Tamura, S. Sato and Y. Hagase, *Chem. Pharm. Bull.*, **36**, 4755 (1988).

333. E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Shell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Merhi, J. Poisson, N. Kunesh and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4490 (1973).

334. A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

335. C. J. Cavallito and T. H. Haskel, *J. Am. Chem. Soc.*, **66**, 1927 (1944).

336. G. W. Kenner and M. A. Murray, *J. Chem. Soc. Suppl.*, 178 (1949).

337. P. N. Rylander, " Catalytic Hydrogenation over Platinum Metals", pp. 46-54, 89-91, 131, 143-148, 169-170, Academic Press, New York, 1967.

338. H. O. House, "Modern Synthetic Reactions", 2nd Edn., p. 3, Benjamin/Cummins Publishing Company, Massachusetts, 1972.

339. Z. Talik and E. Plazek, Acta Pol. Pharm., **12**, 5 (1955); *Chem. Abstr.*, **51**, 17911 (1957).

340. S. Hanessian and M. Kagotani, *Synthesis*, 409 (1987).

341. H. Kwart and R. W. Body, *J. Org. Chem.*, **30**, 118 (1965).

342. W. T. Cadwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942).

343. H. King and L. L. Ware, *J. Chem. Soc.* , 873 (1939).

344. R. J. Sundberg, G. Hamilton and C. Trindle, *J. Org. Chem.*, **51**, 3672 (1986).

345. S. K. Dubey and E. E. Knaus, *Heterocycl.* , **24**, 125 (1986).

346. R. E. Lyle, T. L. Marshall and D. L. Comins, *Tetrahedron Lett.*, 1015 (1977).

347. R. E. Lyle and E. White, *J. Org. Chem.*, **36**, 772 (1971).

348. D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, **47**, 4315 (1982).

349. L. Dagnino, M. Sc. Thesis, University of Alberta, Edmonton, 1985.

350. A. T. Nielsen, D. W. Moore, G. M. Muha and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964).

351. A. Bassindale, "The Third Dimension In Organic Chemistry", p.74, John Wiley and Sons, Toronto, 1984.

352. A. F. Casy, L. G. Chatten and K. K. Khullar, *J. Chem. Soc.*, 2491 (1969).

353. T. Cammack and P. C. Reeves, *J. Heterocycl. Chem.*, **23**, 73 (1986).

354. H. Booth, *Tetrahedron* , **22**, 615 (1965).

355. E. L. Eliel, M. H. Giani and T. H. Williams, *Tetrahedron Lett.*, 741 (1962).

356. M. S. Kharash and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Chapter 10, Prentice-Hall, New York, 1954.

357. C. G. Swain, *J. Am. Chem. Soc.*, **69**, 2306 (1947).

358. F. F. Blicke and E. -P. Tso, *J. Am. Chem. Soc.*, **75**, 5587 (1953).

359. E. M. Sultz, C. M. Robb and J. M. Sprague, *J. Am. Chem. Soc.*, **69**, 2454 (1947).

✓

360. A. F. Casy, *Tetrahedron*, **22**, 2711 (1966).

361. A. J. Jones, A. F. Casy and K. M. J. McErlane, *Can. J. Chem.*, **51**, 1782 (1973).

362. A. F. Casy and K. M. J. McErlane, *J. Chem. Soc. Perkin Trans. I*, 726 (1972).

363. C. Janssen, *Chem. Abstr.*, **70**, 115015 (1968).

364. J. A. Colapret, G. Diamantidis, H. K. Spencer, T. C. Spaulding and F. G. Rudo, *J. Med. Chem.* , **32**, 968 (1989).

365. E. K. Fifer, W. M. Davis and R. F. Borne, *Eur. J. Med. Chem.- Chim. Ther.*, **19**, 519 (1984).

366. A. R. Katritzky and O. Rubio, *J. Org. Chem.*, **48**, 4017 (1983).

367. G. Magnus and R. Levine, *J. Am. Chem. Soc.*, **78**, 427 (1956).

368. E. M. Kaiser and J. D. Petty, *Synthesis*, 705 (1975).

369. G. A. Brine, K. G. Boldt, P.-T. Huang, D. K. Sawyer and F. I. Carrol, *J. Heterocycl. Chem.*, **26**, 677 (1989).

370. E. Siegmund, R. Cadmus and G. A. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957).

371. L. C. Hendershot, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1959).

372. K. Fukawa, O. Kawano, M. Hibi, N. Misaka, S. Ohba and Y. Hatanaka, *J. Pharmacol. Methods*, **4**, 251 (1980).

373. G. J. Giesler, Jr. and J. C. Liebeskind, *Pain*, **2**, 43 (1976).

374. H. Wynn, M. Ramesh, W. C. Matowe, M. W. Wolowyk and E.E.Knaus, *Drug Design and Delivery*, **3**, 245 (1988).

375. N. B. Eddy and H. Halbach, *Bull. WHO*, **13**, 937 (1955).

376. M. Ahmad, Ph. D. Thesis , University of London , 1968.

377. D. M. Zimmerman, M. D. Hynes, B. E. Cantrell, L. G. Mendelsohn and J. D. Leander, *Pain*, **4**, Suppl., 151 (1987).

378. M. Hedayatullah and J. C. Hugueny, *Syn. Commun.*, **11**, 643 (1981).

379. B. E. Betts and W. Davey, *J. Chem. Soc.*, 3333 (1961).

380. J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).